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NEWS 3	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS 4	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS 5	FEB 05	German (DE) application and patent publication number format changes
NEWS 6	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS 7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS 8	MAR 03	FRANCEPAT now available on STN
NEWS 9	MAR 29	Pharmaceutical Substances (PS) now available on STN
NEWS 10	MAR 29	WPIFV now available on STN
NEWS 11	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA
NEWS 12	APR 26	PROMT: New display field available
NEWS 13	APR 26	IFIPAT/IFIUDB/IFICDB: New super search and display field available
NEWS 14	APR 26	LITALERT now available on STN
NEWS 15	APR 27	NLDB: New search and display fields available
NEWS 16	May 10	PROUSDDR now available on STN
NEWS 17	May 19	PROUSDDR: One FREE connect hour, per account, in both May and June 2004
NEWS 18	May 12	EXTEND option available in structure searching
NEWS 19	May 12	Polymer links for the POLYLINK command completed in REGISTRY

NEWS EXPRESS	MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
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=> s treatment
L1     7830374 TREATMENT

=> s l1 and autoimmune
L2       51504 L1 AND AUTOIMMUNE

=> s l2 and biodegradable polymers
L3           1 L2 AND BIODEGRADABLE POLYMERS

=> d l3 cbib abs

L3   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2004 ACS on STN
2001:137052   Document No. 134:183507  Immunological tolerance-induction agent.
     Kim, Ho-Youn; Park, Jong-Sang; Ryoo, Zae-Young; Bae, Euiyoung; Lee,
     Woo-Kyoung; Cho, Chul-Soo; Park, Sung-Hwan; Kim, Wan-Uk (S. Korea).  PCT
     Int. Appl. WO 2001012222 A1 20010222, 50 pp.  DESIGNATED STATES: W:  AE,
     AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE,
     ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
     KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
     RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU,
     ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG,
     CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR,
     NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.  APPLICATION: WO
     1999-KR460 19990818.
AB   A method for treating autoimmune diseases by administering
     orally to a mammal suffering from autoimmune diseases particles
     of biodegradable polymers or their complexes with an
     autoimmune antigen is provided.  Only single administration can
     effectively induce oral tolerance to autoimmune diseases,
     resulting in a strong and prolonged suppression of the diseases.


=> s biodegradable polymers
L4       4696 BIODEGRADABLE POLYMERS

=> s l4 and "poly(D-L-lactide-co-glycolide)"
L5         99 L4 AND "POLY(D-L-LACTIDE-CO-GLYCOLIDE)"

=> s l5 and rheumatoid arthritis
L6          0 L5 AND RHEUMATOID ARTHRITIS

=> s l5 and autoimmune
L7          0 L5 AND AUTOIMMUNE

=> s l5 and treatment
L8          4 L5 AND TREATMENT
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=> dup remove l8
PROCESSING COMPLETED FOR L8
L9 3 DUP REMOVE L8 (1 DUPLICATE REMOVED)

=> d l9 1-3 cbib abs

L9 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1
2002:535571 Document No.: PREV200200535571. In vivo drug distribution dynamics in thermoablated and normal rabbit livers from **biodegradable polymers.** Gao, Jinming [Reprint author]; Qian, Feng; Szymanski-Exner, Agata; Stowe, Nicholas; Haaga, John. Cancer-Targeted Drug Delivery Laboratory, Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, 44106, USA. jmg23@po.cwru.edu. Journal of Biomedical Materials Research, (November, 2002) Vol. 62, No. 2, pp. 308-314. print.
CODEN: JBMRBG. ISSN: 0021-9304. Language: English.
AB Image-guided radiofrequency ablation combined with intratumoral drug delivery provides a novel and minimally invasive **treatment** of liver cancers. In this study, the in vivo transport properties of doxorubicin in thermoablated and nonablated rabbit livers were characterized and compared. Doxorubicin was released from polymer implants (millirods) to the ablated and nonablated liver tissue. At different time points, the 2D distribution profiles were quantitatively determined by a fluorescence imaging method. Analysis of the doxorubicin concentration at the ablation boundary showed that it reached a maximum of 49.8 mug/g at 24 h after implantation, which was higher than the reported cytotoxic concentration of doxorubicin (6.4 mug/g) for liver VX-2 cancer cells. This value dropped to 0.4 mug/g at 48 h after implantation due to the depletion of doxorubicin from the polymer millirod. Results also showed that the area of drug distribution was significantly larger in ablated tissue than nonablated tissue. The therapeutic penetration distance was found to be 5.2 mm in thermoablated livers, compared to 1.2 mm in nonablated livers at 24 h. This difference in drug transport properties is attributed to destruction of the vasculature network in the ablated tissue as supported by histological analysis. Consequently, drug washout by blood perfusion is hampered while drug diffusion becomes the dominant process of transport in the ablated tissue. Results from this study provide insightful information on the rational design and development of polymer millirods for intra-tumoral drug delivery applications.

L9 ANSWER 2 OF 3 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:983731 The Genuine Article (R) Number: 620NR. The effect of gamma-irradiation on drug release from bioerodible microparticles: a quantitative **treatment.** Faisant N; Siepmann J (Reprint); Oury P; Laffineur V; Bruna E; Haffner J; Benoit J P. Univ Angers, INSERM, ERIT M 0104, 10 Rue Andre Boquel, F-49100 Angers, France (Reprint); Univ Angers, INSERM, ERIT M 0104, F-49100 Angers, France; Free Univ Berlin, Coll Pharm, D-12169 Berlin, Germany; Ethypharm, F-92213 St Cloud, France. INTERNATIONAL JOURNAL OF PHARMACEUTICS (21 AUG 2002) Vol. 242, No. 1-2, pp. 281-284. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0378-5173. Pub. country: France; Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The two major objectives of this study were: (i) to monitor the effect of different gamma-irradiation doses (4-33 kGy) on the release kinetics from 5-fluorouracil (5-FU)-loaded **poly(D, L-lactide-co-glycolide)** (PLGA)-based microparticles, and (ii) to analyze the obtained experimental data with a new mathematical model giving insight into the occurring mass transport phenomena. Drug release was found to depend significantly on the applied gamma-irradiation dose. Interestingly, the obtained release profiles were all biphasic: a rapid initial drug release phase ("burst") was followed by

a slower, approximately constant drug release phase. Surprisingly, only the initial rapid drug release was accelerated by gamma-irradiation; the subsequent zero-order phase was almost unaffected. Importantly, the new mathematical model which is based on Fick's second law of diffusion and which considers polymer degradation was applicable to all the investigated systems. In addition, the gamma-irradiation dose could be quantitatively related to the resulting drug release rate. In conclusion, diffusion seems to be the dominating release rate controlling mechanism in all cases, with a significant contribution of the polymer degradation process. (C) 2002 Elsevier Science B.V. All rights reserved.

L9 ANSWER 3 OF 3 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:668318 The Genuine Article (R) Number: 229VT. Carboplatin-loaded PLGA microspheres for intracerebral injection: formulation and characterization . Chen W; Lu D R (Reprint). UNIV GEORGIA, COLL PHARM, DEPT PHARMACEUT, ATHENS, GA 30602 (Reprint); UNIV GEORGIA, COLL PHARM, DEPT PHARMACEUT, ATHENS, GA 30602. JOURNAL OF MICROENCAPSULATION (SEP-OCT 1999) Vol. 16, No. 5, pp. 551-563. Publisher: TAYLOR & FRANCIS LTD. ONE GUNPOWDER SQUARE, LONDON EC4A 3DE, ENGLAND. ISSN: 0265-2048. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The purpose of this study is to prepare and characterize injectable carboplatin-loaded poly(D,L-lactic-co-glycolic) acid copolymer (PLGA) microspheres for the intracerebral **treatment** of malignant glioma. The microspheres were prepared by an acetone/mineral oil emulsion and solvent evaporation method. Preparation variables were optimized and the following processing conditions resulted in the highest drug loading and best yields of the microspheres compared with those prepared with the other variables: the PLGA concentration was 8% (w/w) in the internal phase; the emulsifier (Span 80) concentration was 8% (w/w) in the external phase; the ratio of the internal phase: the external phase was 1:8; the stirring speed was 1500 rpm; the emulsion time was 15 min; the solvent evaporation time was 3.75hr. Microspheres so prepared were analysed for size distribution, drug loading, in vitro release and morphological characteristics. The drug release in phosphate buffer solution started with a 10 day slow release period, followed by a fast near zero order release period from 12 to 22 days. The carboplatin release in brain homogenate was slower than in phosphate buffer solution. The morphological changes of the microspheres during the in vitro degradation correlated with the drug relase profile. In conclusion, the carboplatin-loaded PLGA microspheres were specifically prepared to meet the specification as an injectable and biodegradable brain implant.

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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 17:20:29 ON
     15 MAY 2004
L1      7830374 S TREATMENT
L2        51504 S L1 AND AUTOIMMUNE
L3            1 S L2 AND BIODEGRADABLE POLYMERS
L4         4696 S BIODEGRADABLE POLYMERS
L5           99 S L4 AND "POLY(D-L-LACTIDE-CO-GLYCOLIDE)"
L6            0 S L5 AND RHEUMATOID ARTHRITIS
L7            0 S L5 AND AUTOIMMUNE
L8            4 S L5 AND TREATMENT
L9            3 DUP REMOVE L8 (1 DUPLICATE REMOVED)

=> dup remove l5
PROCESSING COMPLETED FOR L5
L10          45 DUP REMOVE L5 (54 DUPLICATES REMOVED)

=> d l10 1-45 cbib abs
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L10 ANSWER 1 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2004:136075 The Genuine Article (R) Number: 770CQ. Preparation and characterization of cationic PLGA nanospheres as DNA carriers. Kumar M N V R (Reprint); Bakowsky U; Lehr C M. Univ Saarland, Dept Biopharmaceut & Pharmaceut Technol, D-66123 Saarbrucken, Germany (Reprint). BIOMATERIALS (MAY 2004) Vol. 25, No. 10, pp. 1771-1777. Publisher: ELSEVIER SCI LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 0142-9612. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Nanoparticles formulated from **biodegradable polymers** such as poly(lactic acid) (PLA) and poly(lactide-co-glycolide) (PLGA) are being extensively investigated as non-viral gene delivery systems due to their controlled release characteristics and biocompatibility. PLGA nanoparticles for DNA delivery are mainly formulated by an emulsion-solvent evaporation technique using PVA as a stabilizer generating negatively charged particles and heterogeneous size distribution. The objective of the present study was to formulate cationically modified PLGA nanoparticles with defined size and shape that can efficiently bind DNA. An Emulsion-diffusion-evaporation technique to make cationic nanospheres composed of biodegradable and biocompatible co-polyester PLGA has been developed. PVA-chitosan blend was used to stabilize the PLGA nanospheres. The nanospheres were characterized by atomic force microscopy (AFM), photon-correlation spectroscopy (PCS), and Fourier transform infrared spectroscopy (FTIR). Zeta potential and gel electrophoresis studies were also performed to understand the surface properties of nanospheres and their ability to condense negatively charged DNA. The designed nanospheres have a zeta potential of 10 mV at pH 7.4 and size under 200 nm. From the gel electrophoresis studies we found that the charge on the nanospheres is sufficient to efficiently bind the negatively charged DNA electrostatically. These cationic PLGA nanospheres could serve as potential alternatives of the existing negatively charged nanoparticles. (C) 2003 Elsevier Ltd. All rights reserved.

L10 ANSWER 2 OF 45 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2004:176658 Document No.: PREV200400178580. Critical determinants in PLGA/PLA nanoparticle-mediated gene expression. Prabha, Swayam; Labhasetwar, Vinod [Reprint Author]. Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE, 68198, USA. vlabhase@unmc.edu. Pharmaceutical Research (Dordrecht), (February 2004) Vol. 21, No. 2, pp. 354-364. print.
ISSN: 0724-8741 (ISSN print). Language: English.

AB Purpose: The aim of the study was to determine the critical determinants in nanoparticle-mediated gene transfection. It was hypothesized that different formulation parameters could affect the nanoparticle characteristics and hence its gene transfection. Methods: Nanoparticles encapsulating plasmid DNA encoding for firefly luciferase were formulated using polylactide (PLA) and **poly (D,L-lactide-co-glycolide)** (PLGA) polymers of different compositions and molecular weights. A multiple-emulsion solvent-evaporation method with polyvinyl alcohol (PVA) as an emulsifier was used to formulate DNA-loaded nanoparticles. Gene expression of nanoparticles was determined in breast cancer (MCF-7) and prostate cancer (PC-3) cell lines. Results: Nanoparticles formulated using PLGA polymer demonstrated greater gene transfection than those formulated using PLA polymer, and this was attributed to the higher DNA release from PLGA nanoparticles. Higher-molecular-weight PLGA resulted in the formation of nanoparticles with higher DNA loading, which demonstrated higher gene expression than those formulated with lower-molecular-weight PLGA. In addition, the nanoparticles with lower amount of surface-associated PVA demonstrated higher gene transfection in both the cell lines. Higher gene transfection with these nanoparticles was attributed to their higher intracellular uptake and cytoplasmic levels. Further study demonstrated that the molecular weight and the degree of hydrolyzation of PVA used as an emulsifier also affect the gene expression of nanoparticles.

Conclusions: Results thus demonstrate that the DNA loading in nanoparticles and its release, and the surface-associated PVA influencing the intracellular uptake and endolysosomal escape of nanoparticles, are some of the critical determinants in nanoparticle-mediated gene transfection.

L10 ANSWER 3 OF 45 MEDLINE on STN DUPLICATE 1
2004136716. PubMed ID: 15002991. Optimization and characterization of dextran membranes prepared by electrospinning. Jiang Hongliang; Fang Dufei; Hsiao Benjamin S; Chu Benjamin; Chen Weiliam. (Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, New York 11794-2580, USA.) Biomacromolecules, (2004 Mar-Apr) 5 (2) 326-33. Journal code: 100892849. ISSN: 1525-7797. Pub. country: United States. Language: English.

AB Dextran is soluble in both water and organic solvents, so it could be a versatile biomacromolecule for preparing nanofibrous electrospun membranes by blending with either water-soluble bioactive agents or hydrophobic **biodegradable polymers** for biomedical applications. We have formulated electrospun dextran membranes, and the effects of various processing parameters on the membrane properties were investigated. It was found that uniform nanofibrous dextran membranes could be formed by using water, DMSO/water, and DMSO/DMF mixtures as solvents through adjusting the processing conditions (solution concentration, voltage, and the distance between the electrode and the collecting plate). When water was used as a solvent, up to 10% (w/w) of bovine serum albumin (BSA) or lysozyme could be directly incorporated into the dextran electrospun membrane without compromising its morphology. No significant effect of the electrospinning process on lysozyme activity was observed. The composite electrospun membranes consisting of **poly(D, L-lactide-co-glycolide)** (PLGA) and dextran were obtained using DMSO/DMF (50/50, volume ratio) mixture as solvents. For cross-linking the electrospun membrane, dextran was modified by substitution of methacrylate groups at the hydroxyl sites. It was found that the electrospun membranes prepared from methacrylated dextran can be cured by UV irradiation in the presence of 1% of 2,2-dimethoxy-2-phenylacetophenone (DMPA) as a photoinitiator.

L10 ANSWER 4 OF 45 CAPLUS COPYRIGHT 2004 ACS on STN
2004:12097 Production and surface modification of polylactide-based polymeric scaffolds for soft-tissue engineering. Cao, Yang; Croll, Tristan I.; Cooper-White, Justin J.; O'Connor, Andrea J.; Stevens, Geoffrey W. (Department of Chemical and Biomolecular Engineering, The University of Melbourne, Victoria, Australia). Methods in Molecular Biology (Totowa, NJ, United States), 238(Biopolymer Methods in Tissue Engineering), 87-111 (English) 2004. CODEN: MMBIED. ISSN: 1064-3745. Publisher: Humana Press Inc..

AB The two categories of biocompatible, **biodegradable polymers**, such as naturally derived materials and synthetic materials, which have been widely used as scaffold materials for tissue engineering are described. The fabrication of three-dimensional **poly(D,L-lactide-co-glycolide)** scaffolds by the technique solvent casting and particulate leaching, and thermally induced phase separation is also described.

L10 ANSWER 5 OF 45 MEDLINE on STN DUPLICATE 2
2003306710. PubMed ID: 12834581. Monitoring the degradation process of biopolymers by ultrasonic longitudinal wave pulse-echo technique. Wu Hsueh-Chang; Shen Fu-Wen; Hong Xuan; Chang Wenji V; Winet Howard. (Department of Chemical Engineering, University of Southern California, Los Angeles, CA 90089-1211, USA.) Biomaterials, (2003 Oct) 24 (22) 3871-6. Journal code: 8100316. ISSN: 0142-9612. Pub. country: England: United Kingdom. Language: English.

AB A non-destructive ultrasonic longitudinal wave pulse-echo technique was utilized to monitor the degradation process of three **biodegradable polymers**: poly(glycolic acid) (PGA), poly(L-lactic acid) (PLLA)

and 50:50 **poly(D,L-lactide-co-glycolide)** (PDLLG). The degradation processes of PGA and PLLA, which have different molecular structure, were also studied by differential scanning calorimetry (DSC). The degradation processes of PDLLG specimens prepared by different methods were characterized by the ultrasonic wave technique and gel permeation chromatography (GPC). The resulting acoustic and thermal properties indicate that PLLA and PGA exhibit distinctly different degradation behavior, whereas the acoustic properties and molecular weight of PDLLG are sensitive with preparation methods. The present study demonstrates that ultrasonic wave technique provides a powerful tool in detecting the property changes of **biodegradable polymers** prepared with different manufacturing process and that the degradation behavior of **biodegradable polymers** can be closely monitored by ultrasonic technique.

L10 ANSWER 6 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 3
2003:836039 The Genuine Article (R) Number: 724TV. Polymeric nanoparticles based on polylactide and related copolymers. Chiellini E (Reprint); Covolan V L; Orsini L M; Solaro R. Univ Pisa, Dipartimento Chim & Chim Ind, UdR, INSTM Consortium, Via Risorgimento 35, I-56126 Pisa, Italy (Reprint); Univ Pisa, Dipartimento Chim & Chim Ind, UdR, INSTM Consortium, I-56126 Pisa, Italy. MACROMOLECULAR SYMPOSIA (JUL 2003) Vol. 197, pp. 345-354. Publisher: WILEY-V C H VERLAG GMBH. PO BOX 10 11 61, D-69451 WEINHEIM, GERMANY. ISSN: 1022-1360. Pub. country: Italy. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The preparation of nanoparticle suspensions was carried out by using commercial **biodegradable polymers** as poly(d,l-lactide), **poly(d,l-lactide-co-glycolide)** and poly(d,l-lactide-co-epsilon-caprolactone). The method of preparation was based on the controlled addition of polymer organic solution to an aqueous phase containing dispersing agents. Poly(ethylene glycol) (10, 20, and 35 kDa grade), Tween 20, and Pluronic F-127 were used as dispersing agents in the aqueous phase. Content and type of both polymeric matrix and dispersing agent resulted of paramount relevance for the attainment of monodispersed nanoparticles with average diameter of about 130 nm. The addition of a steric stabilizer allowed for nanoparticle purification and isolation while preventing their agglomeration. The best results were obtained by using 35 kDa grade poly(ethylene glycol) as dispersing agent and either mannitol or glycidylisopropylidenglyceryl-beta-cyclodextrin as steric stabilizer. The adopted procedure afforded biodegradable nanoparticle suspensions that could be used for the incapsulation and intravenous administration of biologically active proteins and oligopeptides.

L10 ANSWER 7 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 4
2004:264593 The Genuine Article (R) Number: 800VR. Local drug delivery system using **biodegradable polymers.** Khang G (Reprint); Rhee J M; Jeong J K; Lee J S; Kim M S; Cho S H; Lee H B. Chonbuk Natl Univ, Dept Polymer Sci & Technol, 664-14 Duckjin Dong 1, Jeonju 561756, South Korea (Reprint); Chonbuk Natl Univ, Dept Polymer Sci & Technol, Jeonju 561756, South Korea; Samcheondang Pharm Co Ltd, Res Ctr, Seoul 105037, South Korea; Korea Res Inst Chem Technol, Biomat Lab, Taejon 305606, South Korea. MACROMOLECULAR RESEARCH (AUG 2003) Vol. 11, No. 4, pp. 207-223. Publisher: POLYMER SOC KOREA. ROOM 601, HATCHON BUILDING, 831 YEOKSAM-DONG, KANGNAM-KU, SEOUL 135-792, SOUTH KOREA. ISSN: 1598-5032. Pub. country: South Korea. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB For last five years, we are developing the novel local drug delivery devices using **biodegradable polymers**, especially polylactide (PLA) and. **poly(D,L-lactide-co-glycolide)** (PLGA) due to its relatively good biocompatibility, easily controlled biodegradability, good processability and only FDA approved synthetic degradable polymers. The

relationship between various kinds of drug [water soluble small molecule drugs : gentamicin sulfate (GS), fentanyl citrate (FC), BCNU, azidothymidine (AZT), pamidronate (ADP), 1,25(OH)(2) vitamin D-3, water insoluble small molecule drugs: fentanyl, ipriflavone (IP) and nifedipine, and water soluble large peptide molecule drug: nerve growth factor (NGF), and Japanese encephalitis virus (JEV)], different types of geometrical devices [microspheres (MSs), microcapsule, nanoparticle, wafers, pellet, beads, multiple-layered beads, implants, fiber, scaffolds, and films], and pharmacological activity are proposed and discussed for the application of pharmaceutics and tissue engineering. Also, local drug delivery devices proposed in this work are introduced in view of preparation method, drug release behavior, biocompatibility, pharmacological effect, and animal studies. In conclusion, we can control the drug release profiles varying with the preparation, formulation and geometrical parameters. Moreover, any types of drug were successfully applicable to achieve linear sustained release from short period (1similar to3 days) to long period (over 2 months). It is very important to design a suitable formulation for the wanting period of bioactive molecules loaded in **biodegradable polymers** for the local delivery of drug. The drug release is affected by many factors such as hydrophilicity of drug, electric charge of drug, drug loading amount, polymer molecular weight, the monomer composition, the size of implants, the applied fabrication techniques, and so on. It is well known that the commercialization of new drug needs a lot of cost of money (average: over 10 million US dollar per one drug) and time (average: above 9 years) whereas the development of DDS and high effective generic drug might be need relatively low investment with a short time period. Also, one core technology of DDS can be applicable to many drugs for the market needs. From these reasons, the DDS research on potent generic drugs might be suitable for less risk and high return.

L10 ANSWER 8 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:831503 The Genuine Article (R) Number: 724MK. Polymer degradation and in vitro release of a model protein from **poly(D,L -lactide-co-glycolide)** nano- and microparticles. Panyam J; Dali M A; Sahoo S K; Ma W X; Chakravarthi S S; Amidon G L; Levy R J; Labhasetwar V (Reprint). Univ Nebraska, Med Ctr, Dept Pharmaceut Sci, 600 S 42nd St, Omaha, NE 68198 USA (Reprint); Univ Nebraska, Med Ctr, Dept Pharmaceut Sci, Omaha, NE 68198 USA; Univ Michigan, Coll Pharm, Ann Arbor, MI 48109 USA; Univ Penn, Sch Med, Dept Pediat, Childrens Hosp Philadelphia, Div Cardiol, Philadelphia, PA 19104 USA; Univ Nebraska, Med Ctr, Dept Biochem & Mol Biol, Omaha, NE 68198 USA. JOURNAL OF CONTROLLED RELEASE (19 SEP 2003) Vol. 92, No. 1-2, pp. 173-187. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS . ISSN: 0168-3659. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The objective of the study was to investigate the effect of particle size of nano- and rnicroparticles formulated from **poly(D ,L-lactide-co-glycolide)** (50:50 PLGA) on polymer degradation and protein release. Since the surface area to volume ratio is inversely proportional to the particle size, it is hypothesized that the particle size would influence the polymer degradation as well as the release of the encapsulated protein. PLGA nano- and microparticles of approximate mean diameters of 0.1, 1 and 10 mum, containing bovine serum albumin as a model protein, were formulated using a multiple water-in-oil-in-water emulsion solvent evaporation technique. These particles were incubated at 37 degreesC in phosphate-buffered saline (pH 7.4, 154 mM) and the particles were characterized at various time points for molecular weight of polymer, surface-associated polyvinyl alcohol content (PVA), and the particle surface topology using scanning electron microscopy. The supernatants from the above study were analyzed for the released protein and PVA content. Polymer degradation was found to be biphasic in both nano- and microparticles, with an initial rapid degradation for 20-30 days followed by a slower degradation phase. The 0.1 mum diameter nanoparticles demonstrated relatively higher polymer degradation rate (P<0.05) during the initial phase as compared to the

larger size microparticles (first order degradation rate constants of 0.028 day(-1), 0.011 day(-1) and 0.018 day(-1) for 0.1, 1 and 10 mum particles, respectively), however the degradation rates were almost similar (0.008 to 0.009 day(-1)) for all size particles during the later phase. All size particles maintained their structural integrity during the initial degradation phase; however, this was followed by pore formation, deformation and fusion of particles during the slow degradation phase. Protein release from 0.1 and 1 mum particles was greater than that from 10 mum size particles. In conclusion, the polymer degradation rates in vitro were not substantially different for different size particles despite a 10- and 100-fold greater surface area to volume ratio for 0.1 pm size nanoparticles as compared to 1 and 10 mum size microparticles, respectively. Relatively higher amounts of the surface-associated PVA found in the smaller-size nanoparticles (0.1 mum) as compared to the larger-size microparticles could explain some of the observed degradation results with different size particles.

L10 ANSWER 9 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:802732 The Genuine Article (R) Number: 719EC. Fluorescence and electron microscopy probes for cellular and tissue uptake of **poly(D,L-lactide-co-glycolide)** nanoparticles. Panyam J; Sahoo S K; Prabha S; Bargar T; Labhasetwar V (Reprint). Univ Nebraska, Med Ctr, Dept Pharmaceut Sci, 600 S 42nd St, Omaha, NE 68198 USA (Reprint); Univ Nebraska, Med Ctr, Dept Pharmaceut Sci, Omaha, NE 68198 USA; Univ Nebraska, Med Ctr, Dept Genet Cell Biol & Anat, Omaha, NE 68198 USA; Univ Nebraska, Med Ctr, Dept Biochem & Mol Biol, Omaha, NE 68198 USA. INTERNATIONAL JOURNAL OF PHARMACEUTICS (27 AUG 2003) Vol. 262, No. 1-2, pp. 1-11. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0378-5173. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Nanoparticles formulated from **Poly(D,L-lactide-co-glycolide)** (PLGA) and poly(lactide) (PLA) are being extensively investigated for different therapeutic applications such as for sustained drug, vaccine, and gene delivery. For many of these applications, it is necessary to study the intracellular distribution as well as the tissue uptake of nanoparticles to optimize the efficacy of the encapsulated therapeutic agent. Fluorescence and electron microscopic techniques are usually used for the above purposes. Colloidal gold particles and fluorescent polystyrene, which are generally used as model particles for electron and fluorescence microscopy, respectively, may not be suitable alternatives to PLGA/PLA nanoparticles for these studies mainly because of the differences in their physical properties and also because they do not contain any therapeutic agent. The aim of the present study was to develop and characterize PLGA nanoparticle formulations that would be suitable for confocal/fluorescence and transmission electron microscopic (TEM) Studies. Towards this objective, PLGA nanoparticles containing 6-coumarin as a fluorescent marker and osmium tetroxide as an electron microscopic marker with bovine serum albumin (BSA) as a model protein were formulated. Different physical properties of marker-loaded nanoparticles such as particle size, zeta potential, residual PVA content and protein-loading were compared with those of unloaded nanoparticles and were found to be not significantly different. Furthermore, marker-loaded nanoparticle formulations were non-toxic to the cells as unloaded nanoparticles. Nanoparticles loaded with 6-coumarin were found to be useful for studying intracellular nanoparticle uptake and distribution using confocal microscopy while osmium tetroxide-loaded nanoparticles were found to be useful for studying nanoparticle uptake and distribution in cells and tissue using TEM. It was concluded that 6-coumarin and osmium tetroxide could serve as useful fluorescence and electron microscopy probes, respectively, for incorporation into nanoparticles to study their cellular and tissue distribution. (C) 2003 Elsevier B.V. All rights reserved.

L10 ANSWER 10 OF 45 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:124349 Document No.: PREV200300124349. Intracellular drug delivery using **poly(D,L-lactide-co-glycolide)** nanoparticles derivatized with a peptide from a transcriptional activator protein of HIV-1. Nam, Yoon Sung [Reprint Author]; Park, Ju Young; Han, Sang-Hoon; Chang, Ih-Seop. Amore Pacific R and D Center, 314-1, Bora-ri, Giheung-eup, Yongin-si, Gyounggi-do, 449-729, South Korea. ysnam@pacific.co.kr. Biotechnology Letters, (December 2002) Vol. 24, No. 24, pp. 2093-2098. print.
CODEN: BILED3. ISSN: 0141-5492. Language: English.

AB Biodegradable **poly(D,L-lactide-co-glycolide)** (PLGA) nanoparticles were derivatized with Tat49-57 peptide, which is the protein transduction domain from the transcriptional activator Tat protein of human immunodeficiency virus type-1 (HIV-1). The Tat49-57 peptide-modified PLGA nanoparticles, with a mean diameter of ca. 238 nm, was effectively adsorbed on to the membrane of HaCaT cells and delivered into the nuclei without cytotoxicity.

L10 ANSWER 11 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:144583 The Genuine Article (R) Number: 640GA. Biodegradable comb polyesters containing polyelectrolyte backbones facilitate the preparation of nanoparticles with defined surface structure and bioadhesive properties . Breitenbach A; Jung T; Kamm W; Kissel T (Reprint). Univ Marburg, Dept Pharmaceut & Biopharm, Marburg, Germany (Reprint). POLYMERS FOR ADVANCED TECHNOLOGIES (OCT-DEC 2002) Vol. 13, No. 10-12, pp. 938-950. Publisher: JOHN WILEY & SONS LTD. BAFFINS LANE CHICHESTER, W SUSSEX PO19 1UD, ENGLAND . ISSN: 1042-7147. Pub. country: Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A major challenge in oral peptide and protein delivery remains the search for suitable carrier systems. Therefore, a new concept was investigated combining a modified three-dimensional architecture, increased hydrophilicity of poly(lactic-co-glycolic acid) (PLGA) and charged groups in a single polymer. Biodegradable comb PLGA were synthesized by grafting short PLGA chains onto different poly(vinyl alcohol) (PVA) based backbone polyols, poly(2-sulfobutyl-vinyl alcohol) and poly(diethylaminoethyl-vinyl alcohol). The polyelectrolyte backbones were obtained by etherification of PVA with charge-containing pendent groups. The comb polymer structure could be confirmed by nuclear magnetic resonance, infrared spectroscopy, differential scanning calorimetry, elemental analysis and measurement of intrinsic viscosity. Nanoparticles (NP), as potential mucosal carriers systems, were prepared by controlled precipitation and investigated as a function of polymer composition. The amphiphilic character and the three dimensional architecture of the novel polyesters allowed the preparation of small nanoparticles even without the use of surfactants. Surface NMR, surface charge and hydrophobicity determination indicate a core-corona-like NP structure, especially in the case of negatively charged polyesters. A structural model is proposed for the NP with an inner polyester core and an outer charged-groups-containing surface, depending on polymer composition and backbone charge density. The higher the polymer backbone charge density, the more pronounced its influence on the nanoparticle surface properties. The possibility of preparing NP without the use of a surfactant, as well as of designing the NP surface characteristics by polymer backbone charge density and polymer hydrophilic-hydrophobic balance, will be a major advantage in protein adsorption, bioadhesion and organ distribution. This makes these **biodegradable polymers** promising candidates for colloidal protein and peptide delivery. Copyright (C) 2003 John Wiley Sons, Ltd.

L10 ANSWER 12 OF 45 MEDLINE on STN DUPLICATE 5
2002638066. PubMed ID: 12396384. Biodegradable bromocryptine mesylate microspheres prepared by a solvent evaporation technique. I: Evaluation of formulation variables on microspheres characteristics for brain delivery. Arica B; Kas H S; Orman M N; Hincal A A. (Hacettepe University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 06100 Sihhiye-Ankara,

Turkey.) Journal of microencapsulation, (2002 Jul-Aug) 19 (4) 473-84. Journal code: 8500513. ISSN: 0265-2048. Pub. country: England: United Kingdom. Language: English.

AB The aim of this study was to formulate biodegradable microspheres containing an anti-parkinsonian agent, bromocryptine mesylate, for brain delivery. The effect of formulation parameters (e.g. polymer, emulsifying agent type and concentration) on the characteristics of the microspheres produced, the efficiency of drug encapsulation, the particle size distribution and in vitro drug release rates from the bromocryptine mesylate microspheres were investigated using a 3(2) factorial design. Bromocryptine mesylate was encapsulated into **biodegradable polymers** using the following three different polymers; poly(L-lactide), poly(D,L-lactide) and **poly(D, L-lactide-co-glycolide)**. The SEM photomicrographs showed that the morphology of the microspheres greatly depended on the polymer and emulsifying agent. The results indicate that, regardless of the polymer type, increase in emulsifying agent concentration from 0.25-0.75% w/v markedly decreases the particle size of the microspheres. Determination of particle size revealed that the use of 0.75% w/v of emulsifying agent concentration and a polymer solution concentration of 10% w/v resulted in optimum particle size. In order to prepare biodegradable microspheres with high drug content and small particle size, selection of polymer concentration as well as emulsifying agent concentration is critical. Polymer type has a less pronounced effect on the percentage encapsulation efficiency and particle size of microspheres than on the t(50%). The microspheres prepared by all three polymers, at a polymer concentration of 10% w/v and an emulsifying agent concentration of 0.75% w/v with NaCMC:SO (4:1, w/v) mixture was as the optimum formulation.

L10 ANSWER 13 OF 45 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 6

2002:535571 Document No.: PREV200200535571. In vivo drug distribution dynamics in thermoablated and normal rabbit livers from **biodegradable polymers.** Gao, Jinming [Reprint author]; Qian, Feng; Szymanski-Exner, Agata; Stowe, Nicholas; Haaga, John. Cancer-Targeted Drug Delivery Laboratory, Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, 44106, USA. jmg23@po.cwru.edu. Journal of Biomedical Materials Research, (November, 2002) Vol. 62, No. 2, pp. 308-314. print.
CODEN: JBMRBG. ISSN: 0021-9304. Language: English.

AB Image-guided radiofrequency ablation combined with intratumoral drug delivery provides a novel and minimally invasive treatment of liver cancers. In this study, the in vivo transport properties of doxorubicin in thermoablated and nonablated rabbit livers were characterized and compared. Doxorubicin was released from polymer implants (millirods) to the ablated and nonablated liver tissue. At different time points, the 2D distribution profiles were quantitatively determined by a fluorescence imaging method. Analysis of the doxorubicin concentration at the ablation boundary showed that it reached a maximum of 49.8 mug/g at 24 h after implantation, which was higher than the reported cytotoxic concentration of doxorubicin (6.4 mug/g) for liver VX-2 cancer cells. This value dropped to 0.4 mug/g at 48 h after implantation due to the depletion of doxorubicin from the polymer millirod. Results also showed that the area of drug distribution was significantly larger in ablated tissue than nonablated tissue. The therapeutic penetration distance was found to be 5.2 mm in thermoablated livers, compared to 1.2 mm in nonablated livers at 24 h. This difference in drug transport properties is attributed to destruction of the vasculature network in the ablated tissue as supported by histological analysis. Consequently, drug washout by blood perfusion is hampered while drug diffusion becomes the dominant process of transport in the ablated tissue. Results from this study provide insightful information on the rational design and development of polymer millirods for intra-tumoral drug delivery applications.

L10 ANSWER 14 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:983731 The Genuine Article (R) Number: 620NR. The effect of gamma-irradiation on drug release from bioerodible microparticles: a quantitative treatment. Faisant N; Siepmann J (Reprint); Oury P; Laffineur V; Bruna E; Haffner J; Benoit J P. Univ Angers, INSERM, ERIT M 0104, 10 Rue Andre Boquel, F-49100 Angers, France (Reprint); Univ Angers, INSERM, ERIT M 0104, F-49100 Angers, France; Free Univ Berlin, Coll Pharm, D-12169 Berlin, Germany; Ethypharm, F-92213 St Cloud, France. INTERNATIONA L JOURNAL OF PHARMACEUTICS (21 AUG 2002) Vol. 242, No. 1-2, pp. 281-284. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS . ISSN: 0378-5173. Pub. country: France; Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The two major objectives of this study were: (i) to monitor the effect of different gamma-irradiation doses (4-33 kGy) on the release kinetics from 5-fluorouracil (5-FU)-loaded **poly(D, L-lactide-co-glycolide)** (PLGA)-based microparticles, and (ii) to analyze the obtained experimental data with a new mathematical model giving insight into the occurring mass transport phenomena. Drug release was found to depend significantly on the applied gamma-irradiation dose. Interestingly, the obtained release profiles were all biphasic: a rapid initial drug release phase ("burst") was followed by a slower, approximately constant drug release phase. Surprisingly, only the initial rapid drug release was accelerated by gamma-irradiation; the subsequent zero-order phase was almost unaffected. Importantly, the new mathematical model which is based on Fick's second law of diffusion and which considers polymer degradation was applicable to all the investigated systems. In addition, the gamma-irradiation dose could be quantitatively related to the resulting drug release rate. In conclusion, diffusion seems to be the dominating release rate controlling mechanism in all cases, with a significant contribution of the polymer degradation process. (C) 2002 Elsevier Science B.V. All rights reserved.

L10 ANSWER 15 OF 45 MEDLINE on STN DUPLICATE 7
2002173050. PubMed ID: 11897428. Preparation and characterization of sterile and freeze-dried sub-200 nm nanoparticles. Konan Yvette N; Gurny Robert; Allemann Eric. (School of Pharmacy, University of Geneva, 30, quai Ernest Ansermet, CH-1211 Geneva 4 , Switzerland.) International journal of pharmaceutics, (2002 Feb 21) 233 (1-2) 239-52. Journal code: 7804127. ISSN: 0378-5173. Pub. country: Netherlands. Language: English.

AB The feasibility of producing sterile and freeze-dried polyester nanoparticles was investigated. Various **poly(D, L-lactide-co-glycolide)** and poly(D,L-lactide) were selected as **biodegradable polymers.** Using the salting-out procedure, process parameters were optimized to obtain sub-200 nm particles. After purification, the nanoparticle suspensions containing different lyoprotectants were sterilized by filtration. Freeze-drying was performed using vials covered with 0.22 microm membrane filters in order to preserve the suspensions from bacterial contamination. Sterility was assessed on the final product according to pharmacopoeial requirements using the membrane filtration method. With all polymers tested, sub-200 nm particles could be obtained. Nanoparticles with a size as low as 102 nm were prepared with good reproducibility and narrow size distribution. Upon freeze-drying, it appeared that complete redispersion of all types of polyester nanoparticles could be obtained in presence of the lyoprotectants tested such as saccharides while aggregation was observed without lyoprotectant. Sterility testing showed no microbial contamination indicating that sterile nanoparticulate formulations have been achieved.

L10 ANSWER 16 OF 45 MEDLINE on STN DUPLICATE 8
2002421886. PubMed ID: 12176249. Submicronparticles from **biodegradable polymers.** Jobmann Monika; Rafler Gerald. (Fraunhofer-Institut fur Angewandte Polymerforschung, Geiselbergstrasse 69, 14476, Golm, Germany.. jobmann@iap.fhg.de) . International journal of pharmaceutics, (2002 Aug 21) 242 (1-2) 213-7. Journal code: 7804127.

ISSN: 0378-5173. Pub. country: Netherlands. Language: English.

AB The objective was to prepare small particles in the nm range with poly(D,L-lactide) and **poly(D,L-lactide-co-glycolide)** applying the spontaneous emulsification process. Polymer parameters as well as process parameters were investigated. The results show that spontaneous emulsification is a simple method to produce small particles in the 200-1000 nm range. A major drawback is the limitation to very restricted conditions, e.g. molecular weight up to 30.000 g/mole, glycolide content in the copolymer up to 30 mole% and concentration of the polymer solution lower than or equal to 1% (w/v).

L10 ANSWER 17 OF 45 MEDLINE on STN DUPLICATE 9

2002447975. PubMed ID: 12204570. Size-dependency of nanoparticle-mediated gene transfection: studies with fractionated nanoparticles. Prabha Swayam; Zhou Wen-Zhong; Panyam Jayanth; Labhasetwar Vinod. (Department of Pharmaceutical Sciences, 986025 University of Nebraska Medical Center, Omaha, NE 68198-6025, USA.) International journal of pharmaceutics, (2002 Sep 5) 244 (1-2) 105-15. Journal code: 7804127. ISSN: 0378-5173. Pub. country: Netherlands. Language: English.

AB Nanoparticles formulated from **biodegradable polymers** such as poly (lactic acid) and **poly (D,L-lactide-co-glycolide)** (PLGA) are being extensively investigated as non-viral gene delivery systems due to their sustained release characteristics and biocompatibility. PLGA nanoparticles for DNA delivery are mainly formulated using an emulsion-solvent evaporation technique. However, this formulation procedure results in the formation of particles with heterogeneous size distribution. The objective of the present study was to determine the relative transfectivity of the smaller- and the larger-sized fractions of nanoparticles in cell culture. PLGA nanoparticles containing a plasmid DNA encoding luciferase protein as a marker were formulated by a multiple emulsion-solvent evaporation method (mean particle diameter = 97 +/- 3 nm) and were fractionated using a membrane (pore size: 100 nm) filtration technique. The particles that passed through the membrane were designated as the smaller-sized nanoparticles (mean diameter = 70 +/- 2 nm) and the fraction that was retained on the membrane as the larger-sized nanoparticles (mean diameter = 202 +/- 9 nm). The smaller-sized nanoparticles showed a 27-fold higher transfection than the larger-sized nanoparticles in COS-7 cell line and a 4-fold higher transfection in HEK-293 cell line. The surface charge (zeta potential), cellular uptake, and the DNA release were almost similar for the two fractions of nanoparticles, suggesting that some other yet unknown factor(s) is responsible for the observed differences in the transfection levels. The results suggest that the particle size is an important factor, and that the smaller-sized fraction of the nanoparticle formulation predominantly contributes towards their transfection.

L10 ANSWER 18 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2002:118532 The Genuine Article (R) Number: 517AU. Thermosensitive sol-gel reversible hydrogels. Jeong B; Kim S W; Bae Y H (Reprint). Univ Utah, Dept Pharmaceut & Pharmaceut Chem, Ctr Controlled Chem Delivery, Salt Lake City, UT 84112 USA (Reprint); PNNL, Richland, WA 99352 USA. ADVANCED DRUG DELIVERY REVIEWS (17 JAN 2002) Vol. 54, No. 1, pp. 37-51. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0169-409X. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Aqueous polymer solutions that are transformed into gels by changes in environmental conditions, such as temperature and pH, thus resulting in in situ hydrogel formation, have recently attracted the attention of many investigators for scientific interest and for practical biomedical or pharmaceutical applications. When the hydrogel is formed under physiological conditions and maintains its integrity for a desired period of time, the process may provide various advantages over conventional hydrogels. Because of the simplicity of pharmaceutical formulation by

solution mixing, biocompatibility with biological systems, and convenient administration, the pharmaceutical and biomedical uses of the water-based sol-gel transition include solubilization of low-molecular-weight hydrophobic drugs, controlled release, labile biomacromolecule delivery, such as proteins and genes, cell immobilization, and tissue engineering. When the formed gel is proven to be biocompatible and biodegradable, producing non-toxic degradation products, it will provide further benefits for in vivo applications where degradation is desired. It is timely to summarize the polymeric systems that undergo sol-gel transitions, particularly due to temperature, with emphasis on the underlying transition mechanisms and potential delivery aspects. This review stresses the polymeric systems of natural or modified natural polymers, N-isopropylacrylamide copolymers, poly(ethylene oxide)/poly(propylene oxide) block copolymers, and poly(ethylene glycol)/**poly**(**D,L-lactide-co-glycolide**) block copolymers. (C) 2002 Elsevier Science B.V. All rights reserved.

L10 ANSWER 19 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 10
2001:787415 The Genuine Article (R) Number: 476EN. Phase behavior of **biodegradable polymers** in dimethyl ether and dimethyl ether plus carbon dioxide. Kuk Y M; Lee B C (Reprint); Lee Y W; Lim J S. Hannani Univ, Dept Chem Engn, 133 Ojung Dong, Taejon 306791, South Korea (Reprint); Hannani Univ, Dept Chem Engn, Taejon 306791, South Korea; Korea Inst Sci & Technol, Supercrit Fluids Res Lab, Seoul 136791, South Korea. JOURNAL OF CHEMICAL AND ENGINEERING DATA (SEP-OCT 2001) Vol. 46, No. 5, pp. 1344-1348. Publisher: AMER CHEMICAL SOC. 1155 16TH ST, NW, WASHINGTON, DC 20036 USA. ISSN: 0021-9568. Pub. country: South Korea. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Phase behavior data are presented for **biodegradable polymers** in high-pressure dimethyl ether (DME) and in supercritical mixtures of DME and carbon dioxide (CO2). The cloud point curves of poly(D,L-lactide) MW = 30000) in DME were measured at polymer concentrations up to similar to 15 mass % and at temperatures to 373.15 K and pressures to 14 MPa using a variable-volume view cell apparatus. This system exhibited the characteristics of a lower critical solution temperature phase behavior and showed the pressure-polymer concentration isotherms with the maximum cloud point pressure at the polymer concentration of similar to5 mass %. The cloud point pressure increased with increasing molecular weight of the poly(D,L-lactide). For **poly**(**D,L-lactide-co-glycolide**) copolymers in DME, decreasing the D,L-lactide content in the copolymer caused the single-phase region to shrink and changed the cloud point curve from a lower critical solution temperature behavior to an upper critical solution temperature behavior. The cloud points of poly(D,L-lactide) in the solvent mixtures of DME and CO2 were measured at various CO2 Compositions up to similar to 73 mass % (on a polymer-free basis) and at temperatures up to similar to 373.15 K. As the CO2 Composition in the mixed solvent increased, the cloud point pressure at a fixed temperature increased significantly. Addition Of CO2 to DME caused a lowering of the dissolving power of the mixed solvent due to the decrease of the solvent polarity.

L10 ANSWER 20 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:107249 The Genuine Article (R) Number: 517QC. Wettability of biodegradable surfaces. Vargha-Butler E I (Reprint); Kiss E; Lam C N C; Keresztes Z; Kalman E; Zhang L; Neumann A W. Univ Toronto, Dept Mech & Ind Engn, Toronto, ON M5S 3G8, Canada (Reprint); Lorand Eotvos Univ, Dept Colloid Chem, H-1518 Budapest 112, Hungary; Hungarian Acad Sci, Chem Res Ctr, Dept Surface Sci & Corros Res, H-1525 Budapest, Hungary. COLLOID AND POLYMER SCIENCE (DEC 2001) Vol. 279, No. 12, pp. 1160-1168. Publisher: SPRINGER-VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010 USA. ISSN: 0303-402X. Pub. country: Canada; Hungary. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The study of the interfacial characteristics of **biodegradable**

polymers/copolymers is of importance from the point of view of both surface science and pharmaceutical/ cosmetic applications. Films formed from **biodegradable polymers** allow systematic wettability studies on surfaces with a wide range of copolymer (chemical) compositions. The possibility of interchanging these drug carrier polymers, if their wetting characteristics are similar, could be beneficial to diverse applications. Low-rate dynamic contact angles on films (solvent cast on polar substrates, i.e. on silicon wafer) of poly(lactic acid), and its copolymers with poly(glycolic acid), (with four different copolymer ratios of 85/15, 75/25, 65/35 and 50,150) were measured by axisymmetric drop shape analysis-profile (ADSA-P) with four liquids: water, formamide, 2,2'-thiodiethanol and 3-pyridylcarbinol. The solid surface tensions. gamma(SV), were calculated from the advancing contact angles. 0(A). The surface topography of the polymer films was investigated by atomic force microscopy (AFM). The surface composition of the polymer layers was analyzed by X-ray photoelectron spectroscopy (XPS). The advancing contact angles were found to be independent of the composition of the copolymers, while the receding angles, OR, did decrease with increasing ratio of the polar component [poly(glycolic acid)] in the copolymers. The solid surface tensions calculated from the advancing contact angles of the liquids for all homo- and copolymers were the same within the error limit, the mean value being gamma(SV) = 35.6 +/- 0.2 mJ/m(2) The surface roughness, which was obtained from AFM images, increased with increasing poly(glycolic acid) ratio, without affecting the advancing contact angles. The constancy of gamma(SV) is attributed to the effect of the surface activity of the nonpolar segments of the polymer chains, which oriented to form the outermost layer of the film. This was confirmed by XPS analysis.

L10 ANSWER 21 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:163929 The Genuine Article (R) Number: 400RH. In vitro sustained release of human immunoglobulin G from biodegradable microspheres. Wong H M; Wang J J; Wang C H (Reprint). Natl Univ Singapore, Dept Chem & Environm Engn, 4 Engn Dr 4, Singapore 117576, Singapore (Reprint); Natl Univ Singapore, Dept Chem & Environm Engn, Singapore 117576, Singapore. INDUSTRIAL & ENGINEERING CHEMISTRY RESEARCH (7 FEB 2001) Vol. 40, No. 3, pp. 933-948. Publisher: AMER CHEMICAL SOC. 1155 16TH ST, NW, WASHINGTON, DC 20036 USA. ISSN: 0888-5885. Pub. country: Singapore. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The in vitro controlled release kinetics of human immunoglobulin G (IgG) of different loadings from microspheres of the **biodegradable polymers** poly(L-lactide) (PLA) and **poly(D, L-lactide-co-glycolide)** (PLGA) were investigated. The microspheres were prepared by a double-emulsion technique. The release profiles exhibited an initial burst followed by a period of slow release, with PLA microspheres showing a faster rate of release than PLGA microspheres. The release rate increased with an increase in drug loading. Scanning electron microscopy (SEM) observations revealed wide differences in the morphology of microspheres made from different polymers. Drug loading had no significant effect on the morphology of the microspheres. Laser scanning confocal micrographs demonstrated a homogeneous drug distribution within the microspheres. Results from SEM and mass loss studies revealed no significant extent of polymer erosion after 50 days of release. Modeling studies within the first 50 days of incubation suggested that the mechanisms of drug release were mainly diffusion- and dissolultion-controlled.

L10 ANSWER 22 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:122328 The Genuine Article (R) Number: 397UX. Emulsion copolymerization of D,L-lactide and glycolide in supercritical carbon dioxide. Hile D D; Pishko M V (Reprint). Texas A&M Univ, Dept Chem Engn, 3122 TAMU, College Stn, TX 77843 USA (Reprint); Texas A&M Univ, Dept Chem Engn, College Stn, TX 77843 USA. JOURNAL OF POLYMER SCIENCE PART A-POLYMER CHEMISTRY (15 FEB 2001) Vol. 39, No. 4, pp. 562-570. Publisher: JOHN WILEY & SONS INC. 605 THIRD AVE, NEW YORK, NY 10158-0012 USA. ISSN: 0887-624X. Pub. country: USA

. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Biodegradable polyesters were synthesized via an emulsion polymerization in supercritical carbon dioxide (SC-CO2). Copolymers of lactide and glycolide were synthesized in SC-CO2 with stannous octoate as the ring-opening catalyst and a fluorocarbon polymer surfactant as an emulsifying agent. The conversion of lactide and glycolide was monitored with respect to the reaction time and temperature with H-1 NMR spectroscopy. The conversion of glycolide surpassed 99% within 72 h for an SC-CO2 phase maintained at 200 bar and 70 degreesC. Under the same conditions, lactide conversion reached 65% after 72 h of polymerization. Unpolymerized monomer was removed after the reaction by extraction with an SC-CO2 mobile phase. The molecular weights of all the copolymers were measured by gel permeation chromatography. Weight-average molecular weights (M-w) ranged between 2500 and 30,200 g/mol and polydispersity indices ranged from 1.4 to 2.3 for polymerization times of 6 and 48 h, respectively. Although the molecular weight increased significantly during the first 48 h of reaction, there was no significant difference in the M-w for polymerization times of 48 and 72 h. Emulsion polymerization within the benign solvent SC-CO2 demonstrated improved conversion and molecular weight versus polymers synthesized without surfactant. The emulsion polymerization of lactide and glycolide copolymers in SC-CO2 is proposed as a novel production technique for high-purity, **biodegradable polymers.** (C) 2001 John Wiley & Sons, Inc.

L10 ANSWER 23 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:954664 The Genuine Article (R) Number: 382WM. Physicomechanical properties of biodegradable poly(D,L-lactide) and **poly(D ,L-lactide-co-glycolide)** films in the dry and wet states. Kranz H; Ubrich N; Maincent P; Bodmeier R (Reprint). FREE UNIV BERLIN, COLL PHARM, D-12169 BERLIN, GERMANY (Reprint); FREE UNIV BERLIN, COLL PHARM, D-12169 BERLIN, GERMANY; UNIV H POINCARE, COLL PHARM, F-54001 NANCY, FRANCE. JOURNAL OF PHARMACEUTICAL SCIENCES (DEC 2000) Vol. 89, No. 12, pp. 1558-1566. Publisher: JOHN WILEY & SONS INC. 605 THIRD AVE, NEW YORK, NY 10158-0012. ISSN: 0022-3549. Pub. country: GERMANY; FRANCE. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The objective of this study was to investigate the mechanical properties (% elongation and puncture strength) of poly(D,L-lactide) (PLA) and poly(D,L-lactide-coglycolide) (PLGA) films as a function of exposure time to an aqueous medium and to correlate the mechanical properties to the degradation/erosion of the polymer as a function of the type of polymer [PLA, weight-average molecular weight (M-W) 270,300, or PLGA 50:50, M-W 56,500], the type of plasticizer [(triethyl citrate (TEC) or acetyltributyl citrate (ATBC)], and the exposure time to pH 7.4 phosphate buffer. The glass transition temperature of the films was measured by differential scanning calorimetry (DSC), the molecular weight by size exclusion chromatography (SEC), and the polymer erosion and hydration gravimetrically. The mechanical properties were strongly affected by the type of polymer and plasticizer. PLGA films showed a faster loss of mechanical integrity. TEC, the water-soluble plasticizer, leached from the films, resulting in major differences in the mechanical properties (flexibility) when compared with films plasticized with the more permanent, water-insoluble ATBC. A significant difference in M-W decrease was seen between plasticizer-free and plasticizer-containing PLA films, but not for PLGA films. Plasticized PLA films, which were above their glass transition temperature in the rubbery state, showed a faster decrease in M-W than plasticizer-free PLA ones, which were in the glassy state. The plasticizer addition to the lower M-W PLGA did not enhance the polymer degradation; the plasticizer-free PLGA was already in the rubbery state. Major differences between the two polymers were also seen in the mass loss and the water uptake studies. After 4 weeks, the mass loss was between 2.6 and 7.0% and the water uptake between 10.1 and 21.1% for PLA films, whereas for PLGA films, the mass loss was between 40.3 and 51.3% and the water uptake between 221.9 and 350.6%. 2000 Wiley-Liss, Inc. and

the American Pharmaceutical Association J Pharm Sci 89:1558-1566; 2000.

L10 ANSWER 24 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 11
2000:729383 The Genuine Article (R) Number: 356FH. Cloud points of **biodegradable polymers** in compressed liquid and supercritical chlorodifluoromethane. Lee J M; Lee B C (Reprint); Lee S H. HANNAM UNIV, DEPT CHEM ENGN, TAEDUK GU, 133 OJUNG DONG, TAEJON 306791, SOUTH KOREA (Reprint); HANNAM UNIV, DEPT CHEM ENGN, TAEDUK GU, TAEJON 306791, SOUTH KOREA; LG CHEM LTD, CHEM PROC RES CTR, TAEJON 305380, SOUTH KOREA. JOURNAL OF CHEMICAL AND ENGINEERING DATA (SEP-OCT 2000) Vol. 45, No. 5, pp. 851-856. Publisher: AMER CHEMICAL SOC. 1155 16TH ST, NW, WASHINGTON, DC 20036. ISSN: 0021-9568. Pub. country: SOUTH KOREA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Experimental cloud point curves were measured using a variable-volume view cell apparatus for poly(L-lactide) (L-PLA), poly(D,L-lactide) (D,L-PLA), and **poly(D,L-lactide-co-glycolide)** (D,L-PLG) in high-pressure chlorodifluoromethane (HCFC-22) solvent. All the **biodegradable polymers** studied in this work exhibited a lower critical solution temperature (LCST) phase behavior in HCFC-22. The L-PLA (MW = 2000 g.mol(-1)) was soluble in HCFC-22 over the temperature range of 343.15 to 393.15 K and at pressures of less than 16 MPa. The P-x isotherms and T-x isobars showed a very broad critical region. The L-PLA was observed to become less soluble in HCFC-22 as its molecular weight increased. No differences in the cloud points were observed between the L-PLA and D,L-PLA polymers. When the D,L-lactide content in the D,L-PLG copolymers was decreased, the single-phase region shrunk in size.

L10 ANSWER 25 OF 45 MEDLINE on STN DUPLICATE 12
2000165409. PubMed ID: 10699378. A new method for preparing biodegradable microparticles and entrapment of hydrocortisone in DL-PLG microparticles using supercritical fluids. Ghaderi R; Artursson P; Carlfors J. (Uppsala University, BMC, Department of Pharmaceutics, P.O. Box 580, SE-751 23, Uppsala, Sweden.. raouf.ghaderi@galenik.uu.se) . European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, (2000 Mar) 10 (1) 1-9. Journal code: 9317982. ISSN: 0928-0987. Pub. country: Netherlands. Language: English.
AB An improved process for the production of polymeric microparticles, based on solution-enhanced dispersion by supercritical fluids (SEDS) using a combination of supercritical N(2) and CO(2), was evaluated. The **biodegradable polymers, poly(D, L-lactide-co-glycolide)**: copolymer composition 50:50 (DL-PLG), poly(L-lactide) (L-PLA), poly(D,L-lactide) (DL-PLA) and polycaprolactone, were used for preparation of microparticles by a modified SEDS process. Solutions of the polymers in organic solvents were dispersed and the solvent was extracted with supercritical CO(2) and N(2). The morphology, the size distributions and degree of hydrocortisone entrapment were determined. The combination of supercritical N(2) and CO(2) led to a more efficient dispersion of the polymer solutions than CO(2) alone. This resulted in a reduction of particle size of the microparticles produced from all of the amorphous polymers. Discrete spherical microparticles with a mean volumetric diameter of less than 10 microm were produced from DL-PLG, DL-PLA and L-PLA. Hydrocortisone was successfully entrapped within the DL-PLG microparticles. The modified SEDS process improved the dispersion of amorphous polymer solutions resulting in formation of small spherical microparticles. The SEDS process can be used for incorporation of drugs into the DL-PLG microparticles.

L10 ANSWER 26 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:62894 The Genuine Article (R) Number: 274KK. Porcine insulin biodegradable polyester microspheres: Stability and in vitro release characteristics. Shao P G; Bailey L C (Reprint). RUTGERS STATE UNIV, COLL PHARM, DEPT PHARMACEUT CHEM, 160 FRELINGHUYSEN RD, PISCATAWAY, NJ 08854

(Reprint); RUTGERS STATE UNIV, COLL PHARM, DEPT PHARMACEUT CHEM, PISCATAWAY, NJ 08854; WARNER LAMBERT PARKE DAVIS, DIV RES, MORRIS PLAINS, NJ 07950. PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY (NOV-DEC 2000) Vol. 5, No. 1, pp. 1-9. Publisher: MARCEL DEKKER INC. 270 MADISON AVE, NEW YORK, NY 10016. ISSN: 1083-7450. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The stability of porcine insulin in **biodegradable polymers**, i.e., poly(DL-lactide-co-glycolide) 50:50 (50:50 DL-PLGA) and poly(L-lactide) (L-PLA) was investigated. Insulin encapsulated microspheres were fabricated from both polymers using double-emulsion-solvent evaporation and emulsion-solvent evaporation techniques and subjected to accelerated stability studies at 40 degrees C and 75% relative humidity. Porcine insulin was found to degrade in all microsphere formulations with an average of < 50% of the initial loading amount remaining intact at the end of 4 weeks. The two major degradation products observed in these formulations were determined to be A-21 desamido insulin and covalent insulin dimer with trace amounts of high molecular weight transformation products. In vitro release studies in phosphate buffered saline at 37 degrees C resulted in very slow and incomplete (< 30% in 30 days) release kinetics for all microsphere formulations. Extraction and analyses of the unreleased insulin within the microspheres revealed that an average of similar to 11% of the encapsulated insulin remained intact. The degradation products observed consisted of similar to 15% of three distinct deamidated hydrolysis products including A-21 desamido insulin, similar to 22% covalent insulin dimer, and trace amounts of high molecular weight transformation products. The degradation of porcine insulin within biodegradable polyester microspheres during stability and release studies can be attributed to the gradual decrease in the pH within the microspheres due to progressive polymer hydrolysis resulting in the production of DL-lactic and glycolic acids. The encapsulation of an acid-base indicator, bromophenol blue, in 50:50 PLGA microspheres (as a probe to estimate pH within the microspheres during accelerated stability studies) indicated that the pH decreased to similar to 3.8 after 3 weeks.

L10 ANSWER 27 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:987211 The Genuine Article (R) Number: 266BQ. Human articular chondrocyte adhesion and proliferation on synthetic biodegradable polymer films. IshaugRiley S L (Reprint); Okun L E; Prado G; Applegate M A; Ratcliffe A. ADV TISSUE SCI INC, 10933 N TORREY PINES RD, LA JOLLA, CA 92037 (Reprint). BIOMATERIALS (DEC 1999) Vol. 20, No. 23-24, pp. 2245-2256 . Publisher: ELSEVIER SCI LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 0142-9612. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The effect of polymer chemistry on adhesion, proliferation, and morphology of human articular cartilage (HAC) chondrocytes was evaluated on synthetic degradable polymer films and tissue culture polystyrene (TCPS) as a control. Two-dimensional surfaces of poly(glycolide) (PGA), poly(L-lactide) (L-PLA), poly(D,L-lactide) (D,L-PLA), 85:15 **poly (D,L-lactide-co-glycolide**) (D,L-PLGA), poly(epsilon-caprolactone) (PCL), 90:10 (D,L-lactide-co-caprolactone) (D,L-PLCL), 9:91 D,L-PLCL, 40:60 L-PLCL, 67:33 poly(glycolide-co-trimethylene carbonate) (PGTMC), and poly(dioxanone) (PDO) were made by spin-casting into uniform thin films. Adhesion kinetics were studied using TCPs and PCL films and revealed that the rate of chondrocyte adhesion began to level off after 6 h. Degree of HAC chondrocyte adhesion was studied on all the substrates after 8 h, and ranged from 47 to 145% of the attachment found on TCPS. The greatest number of chondrocytes attached to PGA and 67:33 PGTMC polymer films, and attachment to PCL and L-PLA films was statistically lower than that found on PGA ($p < 0.05$). There was no correlation between amount of chondrocyte attachment to the substrates and the substrates' water contact angle. Chondrocytes proliferated equally well on all the substrates resulting in equivalent cell numbers on all the substrates at both day 4 and day 7 of

the culture. However, these total cell numbers were reached as a result of a 88- and 42-fold expansion on PDO and PLA, respectively, which was significantly higher than the Ii-fold expansion found on TCPS ($p < 0.05$). The greater fold expansion of the cells on PDO and L-PLA films may be attributed to the availability of space for cells to grow, since their numbers at the start of culture were fewer following the 8 h attachment period. This suggests that regardless of initial seeding density on these degradable polymer substrates (i.e., if some minimum number of cells are able to attach), they will eventually populate the surfaces of all these polymers given sufficient space and time.

L10 ANSWER 28 OF 45 MEDLINE on STN DUPLICATE 13
1999396111. PubMed ID: 10468035. Controlled DNA delivery systems. Luo D; Woodrow-Mumford K; Belcheva N; Saltzman W M. (School of Chemical Engineering, Cornell University, Ithaca, New York 14850, USA.) Pharmaceutical research, (1999 Aug) 16 (8) 1300-8. Journal code: 8406521. ISSN: 0724-8741. Pub. country: United States. Language: English.

AB PURPOSE: Genes are of increasing interest as pharmaceuticals, but current methods for long-term gene delivery are inadequate. Controlled release systems using biocompatible and/or **biodegradable polymers** offer many advantages over conventional gene delivery approaches. We have characterized systems for controlled delivery of DNA from implantable polymer matrices (EVAc: poly (ethylene-co-vinyl acetate)) and injectable microspheres (PLGA and PLA: **poly (D, L-lactide-co-glycolide)** copolymer and poly (L-lactide), respectively). METHODS: Herring sperm DNA and bacteria phage lambda DNA were encapsulated as a model system. Released DNA concentration was determined by fluoroassays. Agarose electrophoresis was used to determine the dependence of release rate on DNA size. The Green Fluorescent Protein (GFP) gene was used to determine the integrity and functionality of released DNA. RESULTS: Both small and large DNA molecules (herring sperm DNA, 0.1-0.6 kb; GFP, 1.9 kb; lambda DNA, 48.5 kb) were successfully encapsulated and released from EVAc matrices, and PLGA or PLA microspheres. The release from DNA-EVAc systems was diffusion-controlled. When co-encapsulated in the same matrix, the larger lambda DNA was released more slowly than herring sperm; the rate of release scaled with the DNA diffusion coefficient in water. The chemical and biological integrity of released DNA was not changed. CONCLUSIONS: These low cost, and adjustable, controlled DNA delivery systems, using FDA-approved biocompatible/biodegradable and implantable/injectable materials, could be useful for in vivo gene delivery, such as DNA vaccination and gene therapy.

L10 ANSWER 29 OF 45 SCISEARCH
1999:404245 The Genuine Article (R) Number: 198CY. Preparation of biodegradable microparticles using solution-enhanced dispersion by supercritical fluids (SEDS). Ghaderi R (Reprint); Artursson P; Carlfors J . UPPSALA UNIV, BMC, DEPT PHARMACEUT, POB 580, SE-75123 UPPSALA, SWEDEN (Reprint). PHARMACEUTICAL RESEARCH (MAY 1999) Vol. 16, No. 5, pp. 676-681. Publisher: PLENUM PUBL CORP. 233 SPRING ST, NEW YORK, NY 10013. ISSN: 0724-8741. Pub. country: SWEDEN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose. We have evaluated a new process, involving solution-enhanced dispersion by supercritical fluids (SEDS), for the production of polymeric microparticles.

Methods. The **biodegradable polymers**, Poly (DL-lactide-co-glycolide) : copolymer composition 50:50 (DL-PLG), Poly (L-lactide) (L-PLA), Poly (DL-lactide) (DL-PLA) and Polycaprolactone (PCL), were used for preparation of microparticles using SEDS. Solutions of the polymers in organic solvents were dispersed and sprayed with supercritical CO2. Extraction of the organic solvents resulted in the formation of solid microparticles. The amounts of highly toxic solvents such as dichloromethane (MC) were reduced in the process.

Results. Microparticles were obtained from all polymers. The mean

particle size and shape varied with the polymer used. The morphology of the particles was strongly affected by the choice of polymer solvent. Discrete spherical microparticles of DL-PLG were produced with a mean volumetric diameter of 130 mu m. The microparticles of the L-PLA were almost spherical, and their size increased from 0.5 to 5 mu m as the density of supercritical CO2 decreased. PCL formed microparticles with diameters of 30-210 mu m and showed a strong tendency to form films at high pressure.

Conclusions. The SEDS process appears a promising method for production of microparticles from **biodegradable polymers** without the use of toxic solvents.

L10 ANSWER 30 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

1999:668318 The Genuine Article (R) Number: 229VT. Carboplatin-loaded PLGA microspheres for intracerebral injection: formulation and characterization . Chen W; Lu D R (Reprint). UNIV GEORGIA, COLL PHARM, DEPT PHARMACEUT, ATHENS, GA 30602 (Reprint); UNIV GEORGIA, COLL PHARM, DEPT PHARMACEUT, ATHENS, GA 30602. JOURNAL OF MICROENCAPSULATION (SEP-OCT 1999) Vol. 16, No. 5, pp. 551-563. Publisher: TAYLOR & FRANCIS LTD. ONE GUNPOWDER SQUARE, LONDON EC4A 3DE, ENGLAND. ISSN: 0265-2048. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The purpose of this study is to prepare and characterize injectable carboplatin-loaded poly(D,L-lactic-co-glycolic) acid copolymer (PLGA) microspheres for the intracerebral treatment of malignant glioma. The microspheres were prepared by an acetone/mineral oil emulsion and solvent evaporation method. Preparation variables were optimized and the following processing conditions resulted in the highest drug loading and best yields of the microspheres compared with those prepared with the other variables: the PLGA concentration was 8% (w/w) in the internal phase; the emulsifier (Span 80) concentration was 8% (w/w) in the external phase; the ratio of the internal phase: the external phase was 1:8; the stirring speed was 1500 rpm; the emulsion time was 15 min; the solvent evaporation time was 3.75hr. Microspheres so prepared were analysed for size distribution, drug loading, in vitro release and morphological characteristics. The drug release in phosphate buffer solution started with a 10 day slow release period, followed by a fast near zero order release period from 12 to 22 days. The carboplatin release in brain homogenate was slower than in phosphate buffer solution. The morphological changes of the microspheres during the in vitro degradation correlated with the drug relase profile. In conclusion, the carboplatin-loaded PLGA microspheres were specifically prepared to meet the specification as an injectable and biodegradable brain implant.

L10 ANSWER 31 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

1999:966890 The Genuine Article (R) Number: 264GJ. Biodegradable bromocryptine mesylate microspheres prepared by a solvent evaporation technique II. Suitability for brain and hypophysis delivery. Arica B; Kas H S (Reprint); Sargon M F; Acikgoz B; Hincal A A. HACETTEPE UNIV, FAC PHARM, DEPT PHARMACEUT TECHNOL, TR-06100 ANKARA, TURKEY (Reprint); HACETTEPE UNIV, FAC PHARM, DEPT PHARMACEUT TECHNOL, TR-06100 ANKARA, TURKEY; HACETTEPE UNIV, FAC MED, DEPT ANAT, TR-06100 ANKARA, TURKEY; BAYINDIR MED CTR, TR-06520 SOGUTOZU ANKARA, TURKEY. STP PHARMA SCIENCES (SEP-OCT 1999) Vol. 9, No. 5, pp. 447-455. Publisher: EDITIONS SANTE. 47 RUE GALILEE, 75116 PARIS, FRANCE. ISSN: 1157-1497. Pub. country: TURKEY. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The purpose of the present work, which is focused on the loading of bromocryptine mesylate into biodegradable microspheres with the purpose of prolonging its therapeutic activity, is to study the biodegradation and tissue response after brain and hypophysis tissue implantation. For this purpose, surgery was performed under aseptic conditions. Sprague-Dawley rats were divided into three groups. The rats were anaesthetised with intraperitoneal injections of a ketamine hydrochloride (Ketalar)/xylazine hydrochloride (Romphun) mixture. They received Either blank

poly(L-lactides), poly(D,L-lactides) and poly(D, L-lactidc-co-glycolide) microspheres or bromocryptine mesylate-loaded microspheres ill the brain and hypophysis tissue by intracerebral implication, The right hemisphere was used as a control and the left hemisphere was used as a sample. The rats were sacrificed with all overdose of anaesthetic at 7 days, 14 days and 4 months after the implantation. Histological examinations were performed with light microscopy and transmission electron microscopy. Blank microspheres showed no inflammatory response or other adverse effects in the rat brain and hypophysis and completely biodegraded after 4 months in vivo. No physical signs of toxicity toxicity were shown by the animals receiving bromocryptine mesylate-loaded microspheres. The cellular response was characterized by the presence of fibroblast at day 7. At day 120, the cell reaction was the same as that at day 21. This work: suggests that bromocryptine mesylate-loaded biodegradable microspheres is possibly safe to implant in the mt brain and hypophysis, and that these I,microspheres carl be used in prolonging bromocryptine mesylate release.

L10 ANSWER 32 OF 45 MEDLINE on STN DUPLICATE 14
1999438258. PubMed ID: 10506648. Potential of polymeric lamellar substrate particles (PLSP) as adjuvants for vaccines. Jabbal-Gill I; Lin W; Jenkins P; Watts P; Jimenez M; Illum L; Davis S S; Wood J M; Major D; Minor P D; Li X; Lavelle E C; Coombes A G. (Danbiosyst UK Ltd, Albert Einstein Centre, Highfields Science Park, Nottingham, UK.) Vaccine, (1999 Sep) 18 (3-4) 238-50. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In recent years microspheres or microparticles produced from **biodegradable polymers** such as poly(D,L-lactide) (PLA) and **poly(D, L-lactide-co -glycolide)** (PLGA) containing encapsulated vaccine antigens have been investigated for administration via parenteral, oral, and intranasal routes. These microparticles allow the controlled release of vaccines with an aim to reduce the number of doses for primary immunisation or to develop single dose vaccines. The polymer materials have been widely regarded as being of minimal toxicity. Evaluation of candidate systems in animal studies have shown antibody levels and cell responses similar to or greater than those observed with adjuvants such as alum. However, there are concerns regarding the integrity and immunogenicity of the antigen during the encapsulation process when the antigen is exposed to organic solvents, high shear stresses and the exposure of antigen to low pH which is caused by polymer degradation. An alternative approach would be to adsorb antigens to the surface of biodegradable polymer particles. Polymeric lamellar substrate particles (PLSP), produced by a simple precipitation of PLA, are suitable for this purpose. The adsorption of antigens onto these particles is a simple procedure. It avoids pH changes due to bulk polymer degradation and the use of solvents and therefore will be less damaging to the vaccine. Moreover, such systems will be much easier to scale up for a clinical study and eventual manufacture. The aim of this article is to discuss the preparation and physical characteristics of PLSP, antigen adsorption, in vivo efficacy of PLSP antigen systems and to consider the potential of PLSP as controlled release adjuvants for protein, peptide or viral vaccines.

L10 ANSWER 33 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:223314 The Genuine Article (R) Number: 176UN. Engineering bone regeneration with bioabsorbable scaffolds with novel microarchitecture. Whang K (Reprint); Healy K E; Elenz D R; Nam E K; Tsai D C; Thomas C H; Nuber G W; Glorieux F H; Travers R; Sprague S M. NORTHWESTERN UNIV, SCH MED, DIV BIOL MAT, CHICAGO, IL; NORTHWESTERN UNIV, ROBERT R MCCORMICK SCH ENGN & APPL SCI, DEPT BIOMED ENGN, EVANSTON, IL 60208; NORTHWESTERN UNIV, SCH MED, DEPT ORTHOPAED SURG, CHICAGO, IL 60611; SHRINERS HOSP CRIPPLED CHILDREN, GENET UNIT, MONTREAL, PQ H3G 1A6, CANADA; NORTHWESTERN UNIV, SCH MED, EVANSTON HOSP, DIV NEPHROL, EVANSTON, IL. TISSUE ENGINEERING (SPR 1999) Vol. 5, No. 1, pp. 35-51. Publisher: MARY ANN LIEBERT INC PUBL. 2 MADISON AVENUE, LARCHMONT, NY 10538. ISSN: 1076-3279. Pub. country: USA; CANADA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Critical-sized defects (CSDs) were introduced into rat calvaria to test the hypothesis that absorption of surrounding blood, marrow, and fluid from the osseous wound into a bioabsorbable polymer matrix with unique microarchitecture can induce bone formation via hematoma stabilization. Scaffolds with 90 % porosity, specific surface areas of approximately 10 m(2)/g, and median pore sizes of 16 and 32 mu m, respectively, were fabricated using an emulsion freeze-drying process. Contact radiography and radiomorphometry revealed the size of the initial defects (50 mm(2)) were reduced to 27 +/- 11 mm(2) and 34 +/- 17 mm(2) for CSDs treated with **poly(D,L-lactide-co-glycolide)**. Histology and histomorphometry revealed scaffolds filled with significantly more de novo bone than negative controls ($p < 0.007$), more osteoid than both the negative and autograft controls ($p < 0.002$), and small masses of mineralized tissue (<15 mu m in diameter) observed within the scaffolds. Based on these findings, we propose a change in the current paradigm regarding the microarchitecture of scaffolds for in viva bone regeneration to include mechanisms based on hematoma stabilization.

L10 ANSWER 34 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

1999:362380 The Genuine Article (R) Number: 192PX. Tetracycline-HCl-loaded poly(DL-lactide-co-glycolide) microspheres prepared by a spray drying technique: influence of gamma-irradiation on radical formation and polymer degradation. Bittner B; Mader K; Kroll C; Borchert H H; Kissel T (Reprint). UNIV MARBURG, DEPT PHARMACEUT & BIOPHARM, KETZERBACH 63, D-35032 MARBURG, GERMANY (Reprint); UNIV MARBURG, DEPT PHARMACEUT & BIOPHARM, D-35032 MARBURG, GERMANY; HUMBOLDT UNIV, INST PHARM, D-13086 BERLIN, GERMANY. JOURNAL OF CONTROLLED RELEASE (1 MAY 1999) Vol. 59, No. 1, pp. 23-32. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0168-3659. Pub. country: GERMANY. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Tetracycline-HCl (TCH)-loaded microspheres were prepared From poly(lactide-co-glycolide) (PLGA) by spray drying. The drug was incorporated in the polymer matrix either in solid state or as w/o emulsion. The spin probe 4-hydroxy-2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPOL) and the spin trap tert-butyl-phenyl-nitrone (PBN) were co-encapsulated into the TCH-loaded and placebo particles. We investigated the effects of gamma-irradiation on the formation of free radicals in polymer and drug and the mechanism of chain scission after sterilization. gamma-Irradiation was performed at 26.9 and 54.9 kGy using a Co-60 source. The microspheres were characterized especially with respect to the formation of radicals and in vitro polymer degradation. Electron paramagnetic resonance (EPR) spectroscopy, gel permeation chromatography (GPC), differential scanning calorimetry (DSC), high-performance liquid chromatography (HPLC), gas chromatography-mass spectroscopy (GC-MS), and scanning electron microscopy (SEM) were used for characterization of the microspheres. Using EPR spectroscopy, we successfully detected gamma-irradiation induced free radicals within the TCH-loaded microspheres, while unloaded PLGA did not contain radicals under the same conditions. The relatively low glass transition temperature of the poly(DL-lactide-co-glycolide) (37-39 degrees C) seems to favor subsequent reactions of free radicals due to the high mobility of the polymeric chains. Because of the high melting point of TCH (214 degrees C), the radicals can only be stabilized in drug loaded microspheres. In order to determine the mechanism of polymer degradation after exposure to gamma-rays, the spin trap PEN and the spin probe TEMPOL were encapsulated in the microspheres. gamma-Irradiation of microspheres containing PEN resulted in the formation of a lipophilic spin adduct, indicating that a polymeric radical was generated by random chain scission. Polymer degradation by an unzipping mechanism would have produced hydrophilic spin adducts of PEN and monomeric radicals of lactic or glycolic acid. These degradation products were not detected by EPR. This result is confirmed by the observation that possible diamagnetic reaction products of low

molecular weight, consisting of TEMPOL and lactide or glycolide monomers, could not be detected by GC-MS. While an irradiation dose-dependent decrease in molecular weight of PLGA could be verified in agreement with the literature, TCH content of the microspheres was not affected by the exposure to gamma-rays. It can be concluded that EPR spectroscopy in combination with GPC, DSC, and HPLC allows a detailed characterization of the impact of gamma-sterilization on biodegradable parenteral drug delivery systems. (C) 1999 Elsevier Science B.V. All rights reserved.

L10 ANSWER 35 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:544601 The Genuine Article (R) Number: ZZ152. Controlled drug delivery by biodegradable poly(ester) devices: Different preparative approaches. Jain R (Reprint); Shah N H; Malick A W; Rhodes C T. NANOSYST LLC, 300 HORIZON DR, KING OF PRUSSIA, PA 19406 (Reprint); UNIV RHODE ISL, DEPT APPL PHARMACEUT SCI, KINGSTON, RI 02881; HOFFMANN LA ROCHE INC, PHARMACEUT R&D, NUTLEY, NJ 07110. DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY (JUL 1998) Vol. 24, No. 8, pp. 703-727. Publisher: MARCEL DEKKER INC. 270 MADISON AVE, NEW YORK, NY 10016. ISSN: 0363-9045. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB There has been extensive research on drug delivery by biodegradable polymeric devices since bioresorbable surgical sutures entered the market two decades ago. Among the different classes of **biodegradable polymers**, the thermoplastic aliphatic poly(esters) such as poly(lactide) (PLA), poly(glycolide) (PGA), and especially the copolymer of lactide and glycolide referred to as poly(lactide-co-glycolide) (PLGA) have generated tremendous interest because of their excellent biocompatibility, biodegradability, and mechanical strength. They are easy to formulate into various devices for carrying a variety of drug classes such as vaccines, peptides, proteins, and micromolecules. Most importantly, they have been approved by the United States Food and Drug Administration (FDA) for drug delivery. This review presents different preparation techniques of various drug-loaded PLGA devices, with special emphasis on preparing microparticles. Certain issues about other related biodegradable polyesters are discussed.

L10 ANSWER 36 OF 45 MEDLINE on STN DUPLICATE 15
1999019846. PubMed ID: 9801448. Biocompatibility testing of ABA triblock copolymers consisting of poly(L-lactic-co-glycolic acid) A blocks attached to a central poly(ethylene oxide) B block under in vitro conditions using different L929 mouse fibroblasts cell culture models. Zange R; Li Y; Kissel T. (Department of Pharmaceutics and Biopharmacy, Philipps University of Marburg, Ketzerbach 63, D-35032 Marburg, Germany.) Journal of controlled release : official journal of the Controlled Release Society, (1998 Dec 4) 56 (1-3) 249-58. Journal code: 8607908. ISSN: 0168-3659. Pub. country: Netherlands. Language: English.
AB The biocompatibility of ABA triblock copolymers consisting of poly(L-lactide-co-glycolide) A blocks attached to a central poly(ethylene oxide), (PEO), B block was investigated under in vitro conditions. The ABA triblock copolymer was compared to commercially available **Poly (D,L-lactide-co-glycolide**) (PLGA) and reference materials in different L929 cell culture models according to the procedure recommended by the International Standard Organization (ISO). Different preparation methods: namely extraction, indirect contact and direct contact with polymer samples were compared. The extraction method seems to be the most sensitive assay, allowing estimates of IC50 values. ABA and PLGA polymers showed excellent compatibility with L929 fibroblasts with all preparation techniques used.The influence of polymer composition and molecular weight on degradation rate as well as in vitro biocompatibility was then investigated. Changes in pH and osmolarity as well as lactic acid content of the extracts were determined and compared to in vitro degradation data of polymer films in phosphate buffered saline at 37 degreesC evaluating molecular weight (GPC) and massloss (gravimetry). An acceleration of the degradation rate of the ABA triblock copolymers with increasing PEO content was observed. The in vitro cytotoxicity studies demonstrated that

the three ABA polymers were well tolerated by fibroblasts in cell culture. One ABA polymer batch ABA2 showed unusual in vitro cytotoxicity in L929 fibroblasts, possibly related to the molecular weight of the PEO used for this particular batch or residual glycolic acid.Cell culture models for biocompatibility testing of polymers according to ISO are useful as screening models in characterizing **biodegradable polymers**, but they cannot replace animal testing. The extraction method in combination with the MTT assay allows quantitative ranking of cytotoxic properties with high sensitivity.

L10 ANSWER 37 OF 45 MEDLINE on STN DUPLICATE 16
1999107025. PubMed ID: 9892007. Biocompatibility, cell adhesion, and degradation of surface-modified **biodegradable polymers** designed for the upper urinary tract. Brauers A; Jung P K; Thissen H; Pfannschmidt O; Michaeli W; Hoecker H; Jakse G. (Clinic of Urology, Institute of Textile Chemistry, Medical School of the Technical University, RWTH Aachen, Germany.) Techniques in urology, (1998 Dec) 4 (4) 214-20. Journal code: 9508161. ISSN: 1079-3259. Pub. country: United States. Language: English.

AB OBJECTIVES: The aim of this study was to develop a short bioresorbable ureteric stent and to characterize polymers and their surface modifications with respect to biocompatibility, degradation kinetics, cell adhesion properties, and incorporation of biologically active substances. Poly(D,L-lactide) PDLLA, **poly(D,L-lactide-co-glycolide)** PDLLA-co-GLY, and poly(D,L-lactide-co-trimethylenecarbonate) PDLLA-co-TMC were chosen as basic polymers. Surface modification was performed by plasma-induced graft polymerization and included grafting with hydroxyethylmethacrylate (HEMA), oligo(ethyleneoxide)-monomethacrylate (OEOMA), and acrylic acid (AAC). Biocompatibility of the polymers was assessed in vitro applying parameters of cell morphology, proliferative activity, and cell adhesion. All polymers were biocompatible and exerted no toxic effect on urothelial cell lines and on primary human urothelial cell cultures. A markedly reduced cell adhesion could be achieved in polymers grafted with HEMA, OEOMA, and AAC. Our results indicate that surface modification of bioresorbable polymers by grafting with HEMA, OEOMA, or AAC is an efficient approach to improve surface properties with respect to biocompatibility and cell adhesion properties.

L10 ANSWER 38 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:941367 The Genuine Article (R) Number: 145FN. In vitro degradation study of polyester microspheres by a new HPLC method for monomer release determination. Giunchedi P (Reprint); Conti B; Scalia S; Conte U. UNIV PAVIA, DIPARTIMENTO CHIM FARMACEUT, VIA TARAMELLI 12, PAVIA, ITALY (Reprint); UNIV FERRARA, DIPARTIMENTO SCI FARMACEUT, I-44100 FERRARA, ITALY. JOURNAL OF CONTROLLED RELEASE (4 DEC 1998) Vol. 56, No. 1-3, pp. 53-62. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0168-3659. Pub. country: ITALY. Language: English. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Biodegradable polyesters have increasing importance as materials used for the preparation of microspheres. The knowledge of their degradation process is important to prepare microparticulate delivery systems with suitable drug release rates. In this work an in vitro degradation study of empty and drug loaded microspheres is described. Three different polyesters were used: two poly-D,L-lactides of different molecular weight and a **poly-D,L-lactide-co-glycolide** (50:50). Diazepam has been chosen as the model drug. Solvent evaporation and spray-drying were used as preparation methods. To study the polymer degradation process, a new HPLC method is proposed for the direct and (in the case of the copolymer) simultaneous determination of the monomer(s): lactic acid (LA) and glycolic acid (GA). SEM and particle size analysis highlight the different characteristics of the particles, depending on their preparation method: spray-dried spheres result to be always smaller with respect to particles obtained by solvent evaporation. The results obtained indicate in particular that: the

preparation methods play an important role in determining the degradation behaviour of microspheres, as unloaded spray-dried particles are characterized by a higher monomer release fate with respect to microspheres obtained by solvent evaporation; PLGA spheres degrade faster than PDLLA microparticles, according to the higher hydrophilicity of the copolymer; the two monomers are released at a different rate in the case of PLGA (faster for GA, slower for LA); the presence of diazepam increases the polymer degradation rate, with respect to empty particles. (C) 1998 Elsevier Science BN. All rights reserved.

L10 ANSWER 39 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
97:148749 The Genuine Article (R) Number: WG586. In vitro evaluation of **poly(D,L-lactide-co-glycolide)** polymer-based implants containing the alpha-melanocyte stimulating hormone analog, Melanotan-I. Bhardwaj R; Blanchard J (Reprint). UNIV ARIZONA, COLL PHARM, DEPT PHARMACOL & TOXICOL, TUCSON, AZ 85721 (Reprint); UNIV ARIZONA, COLL PHARM, DEPT PHARMACOL & TOXICOL, TUCSON, AZ 85721. JOURNAL OF CONTROLLED RELEASE (3 MAR 1997) Vol. 45, No. 1, pp. 49-55. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0168-3659. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The release of the melanotropic peptide, Melanotan-I (MT-I), from biodegradable implants of **poly(D,L lactide-co-glycolide)** (PLGA) copolymer was studied. The implants were prepared by a melt-extrusion method. The in vitro release of MT-I exhibited a triphasic profile with an initial rapid release followed by a secondary phase of slow release, then a tertiary phase of rapid release due to erosion of the polymer. The initial rapid release observed with PLGA (50:50 molar ratio of lactic/glycolic acid) polymers was less than 5% of the drug load and the tertiary phase commenced after about 3 weeks. The factors controlling the drug release are degradation and erosion of the polymer which may, in turn, be controlled by the physical properties of the polymer such as molecular weight and viscosity. The influence of viscosity (0.2-1.08 dl/g) of the polymer, on the release kinetics of MT-I were analyzed and the polymer having a viscosity of 0.6 dl/g was selected for preparing a 1-month implant system. Molecular weight distribution analysis indicated a biphasic rate of molecular weight reduction and within 12 days, the molecular weight had decreased to 50% of the initial value. The release rate was examined at different drug loading levels and in the presence of some hydrophilic additives. The effect of gamma radiation on the release kinetics of the peptide was analyzed to determine the optimal radiation sterilization dose for the PLGA implants. There was no significant difference in the total duration of MT-I release between the implants exposed to no radiation and the 2.5 Mrad dose selected.

L10 ANSWER 40 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
96:808107 The Genuine Article (R) Number: VQ135. STABILITY STUDY OF NANOPARTICLES OF POLY(EPSILON-CAPROLACTONE), POLY(D,L-LACTIDE) AND **POLY(D,L-LACTIDE-CO-GLYCOLIDE)**. LEMOINE D (Reprint); FRANCOIS C; KEDZIEREWICZ F; PREAT W; HOFFMAN M; MAINCENT P. UNIV CATHOLIQUE LOUVAIN, UNITE PHARM GALEN, B-1200 BRUSSELS, BELGIUM (Reprint); UNIV NANCY 1, PHARM GALEN & BIOPHARM LAB, NANCY, FRANCE. BIOMATERIALS (NOV 1996) Vol. 17, No. 22, pp. 2191-2197. ISSN: 0142-9612. Pub. country: BELGIUM; FRANCE. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The objective was to evaluate the stability of nanoparticles prepared with poly(epsilon-caprolactone), poly(D,L-lactide) and **poly(D,L-lactide-co-glycolide)** polymers and stored at different temperatures and in different media. The stability parameters studied were molecular weight and crystallinity of the polymer, nanoparticle size and pH. The results show that the stability of polymeric nanoparticles depends on (i) the type of polymers with the

following increasing order of polymer stability: PLA25GA50 < PLA37.5GA25 < PLA50 = PCL, (ii) the storage temperature: PCL and PLA50 nanoparticles can be kept at 4 degrees C and RT during one year, while PLA37.5GA25 and PLA25GA50 nanoparticles have to be stored at 4 degrees C, and (iii) the storage conditions: buffering or freeze-drying nanoparticles improves stability. (C) 1996 Elsevier Science Limited

L10 ANSWER 41 OF 45 MEDLINE on STN DUPLICATE 17
97092524. PubMed ID: 8938242. Non-invasive in vivo characterization of release processes in **biodegradable polymers** by low-frequency electron paramagnetic resonance spectroscopy. Mader K; Gallez B; Liu K J; Swartz H M. (Dartmouth Medical School, Department of Radiology, Hanover, NH 03755, USA.) Biomaterials, (1996 Feb) 17 (4) 457-61. Journal code: 8100316. ISSN: 0142-9612. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Using stable free radicals (nitroxides) whose spectra reflect microviscosity and pH, low-frequency electron paramagnetic resonance (EPR) spectroscopy was used to characterize the release pattern of subcutaneous implants of **poly(D,L-lactide-co-glycolide)** (PLGA) continuously and non-invasively in living mice. No significant changes occurred during the first days after implantation. After about 1 week, the recorded EPR spectra gave direct evidence for the formation of compartments with high mobility and increasing acidity in the delivery system. The contribution of the mobile part of the spectrum increased with time, but no remarkable decay of the overall signal intensity was observed during the second week. The EPR signals decayed rapidly after 3 weeks. The experimental data are consistent with bulk hydrolysis as the dominating mechanism of release and are not consistent with a surface-controlled pattern of degradation. The formation of acidic compartments in the delivery system may have significant effects on drug stability, drug solubility, bioavailability, pharmacokinetics, and ultimately on therapeutic efficiency. In particular, the finding of areas of low pH within the polymer raise the possibility that hydrolysable drugs may undergo degradation in the implant prior to their release. Our results demonstrate that EPR is a valuable tool for characterizing such drug delivery systems in vivo.

L10 ANSWER 42 OF 45 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 18
1997:128473 Document No.: PREV199799420286. Controlled release of levamisole from poly-(epsilon-caprolactone) matrices: III. Effects of molecular weight and polymer coating on drug release. Vandamme, T. F. [Reprint author]; Ngombo Mukendi, J.-F.. Universite Louis Pasteur, Faculte de Pharmacie, Centre de Recherches Pharmaceutiques, Laboratoire de Pharmacie Galenique et de Pharmacotechnie, 74 Route du Rhin, B.P.24, 67401 Illkirch cedex, France. International Journal of Pharmaceutics (Amsterdam), (1996) Vol. 145, No. 1-2, pp. 77-86.
CODEN: IJPHDE. ISSN: 0378-5173. Language: English.

AB Rumino-reticulum devices (RRDs) (oral dosage forms allowing the release of a drug in the first part of the stomach of grazing animals during a prolonged time) in the form of cylindrical matrices were constructed to release orally anthelmintics in large animals during a period of 3-5 months. The aim of this study was to determine the influence of the molecular weight of the poly-(epsilon-caprolactone) (PCL) constituting the polymeric matrix and the influence of coatings on selected RRDs. The influence of the molecular weight and the coating on these RRDs were studied by the rate and the kinetic release of a model anthelmintic compound, levamisole hydrochloride. For the molecular weight, no significant differences (P gt 0.05) were observed for matrix systems with a molecular weight of 101100 or 147000 Da. Conversely, a faster release (P lt 0.05) was observed for a matrix with a molecular weight of 53500 Da. Different kinetic release profiles of levamisole were achieved by application of coatings of poly-(epsilon-caprolactone), poly-(L-lactide) (PLA) and **poly-(D,L-lactide-co-glycolide)** (PLGA). While all coatings of PCL or PLGA

reduced the release rate of the drug, only the coatings with PLA induced a lag time (apprx 15 days) before the release of the drug. The lag time encountered with PLA coatings was attributed to the crystallinity of the polymer. For the RRDs constructed with different molecular weights and those coated with PCL, fractional release as a function of time is shown to fit the Roseman-Higuchi model. Plots of (1- F) In(1-F) + F are linear with time where F is the fraction of drug released at time t. In vitro drug release studies were conducted in conditions as near as possible to those encountered in vivo. Based on the typical pH encountered in vivo, complete release of the drug would ensure good bioavailability of the drug following oral administration.

L10 ANSWER 43 OF 45 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
95:402762 The Genuine Article (R) Number: RB754. GAMMA-IRRADIATION EFFECTS ON MOLECULAR-WEIGHT AND IN-VITRO DEGRADATION OF **POLY(D, L-LACTIDE-CO-GLYCOLIDE)**
MICROPARTICLES. HAUSBERGER A G; KENLEY R A; DELUCA P P (Reprint). UNIV KENTUCKY, COLL PHARM, ROOM 333, LEXINGTON, KY, 40536 (Reprint); UNIV KENTUCKY, COLL PHARM, LEXINGTON, KY, 40536; PFIZER INC, GROTON, CT, 06340; AMYLIN PHARMACEUT INC, SAN DIEGO, CA, 00000. PHARMACEUTICAL RESEARCH (JUN 1995) Vol. 12, No. 6, pp. 851-856. ISSN: 0724-8741. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose. The objective of the reported work was to quantitatively establish gamma-irradiation dose effects on initial molecular weight distributions and in vitro degradation rates of a candidate erodible biopolymeric delivery system. Methods. **Poly(D, L-lactide-co-glycolide)** (PLGA) porous microparticles were prepared by a phase-separation technique using a 50:50 copolymer with 30,000 nominal molecular weight. The microparticles were subjected to 0, 1.5, 2.5, 3.5, 4.5, and 5.5 Mrad doses of gamma-irradiation and examined by size exclusion chromatography (SEC) to determine molecular weight distributions. The samples were subsequently incubated in vitro at 37 degrees C in pH 7.4 PBS and removed at timed intervals for gravimetric determinations of mass loss and SEC determinations of molecular weight reduction. Results. Irradiation reduced initial molecular weight distributions as follows (M(n) values shown parenthetically for irradiation doses): 0 Mrad (M(n) = 25200 Da), 1.5 Mrad (18700 Da), 2.5 Mrad (17800 Da), 3.5 Mrad (13800 Da), 4.5 Mrad (12900 Da), 5.5 Mrad (11300 Da). In vitro degradation showed a lag period prior to zero-order loss of polymer mass. Onset times for mass loss decreased with increasing irradiation dose: 0 Mrad (onset = 3.4 weeks), 1.5 Mrad (2.0 w), 2.5 Mrad (1.5 w), 3.5 Mrad (1.3 w), 4.5 Mrad (1.0 w), 5.5 Mrad (0.8 w). The zero-order mass loss rate was 12%/week, independent of irradiation dose. Onset of erosion corresponded to M(n) = 5200 Da, the point where the copolymer becomes appreciably soluble. Conclusions. The data demonstrated a substantial effect of gamma-irradiation on initial molecular weight distribution and onset of mass loss for PLGA, but no effect on rate of mass loss.

L10 ANSWER 44 OF 45 MEDLINE on STN DUPLICATE 19
95399459. PubMed ID: 7669829. Characterization of biodegradable **poly(D,L-lactide-co-glycolide)** polymers and microspheres. Hausberger A G; DeLuca P P. (University of Kentucky, College of Pharmacy, Lexington 40536-0082, USA.) Journal of pharmaceutical and biomedical analysis, (1995 May) 13 (6) 747-60. Journal code: 8309336. ISSN: 0731-7085. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Characterization of **biodegradable polymers** used for controlled drug delivery is essential to ensure reproducibility of in vitro and in vivo performance. Selected characterization techniques established for **poly(D,L-lactide-co-glycolide)** (PLGA) copolymers included DSC to analyse thermal behavior, 13C-NMR to determine exact comonomer ratios and comonomer sequencing, cloud point titration to establish solubility, SEC

to monitor molecular weight averages and polydispersity, SEM to observe surface morphology, BET gas adsorption to analyse surface area, tapped bulk density measurements to suggest internal pore structure and porosity and finally in vitro degradation to analyse degradation times and profiles. Comonomer ratios of 50:50 PLGAs were found to be closer to stated values for Boehringer Ingelheim polymers than for polymers from two other suppliers. Implementing such a characterization program for **biodegradable polymers** ensures the production of reproducible and reliable controlled drug delivery systems.

L10 ANSWER 45 OF 45 MEDLINE on STN DUPLICATE 20
93195715. PubMed ID: 8450430. Degradation and release properties of pellets fabricated from three commercial **poly(D, L-lactide-co-glycolide) biodegradable polymers.** Schmitt E A; Flanagan D R; Linhardt R J. (Division of Pharmaceutics, College of Pharmacy, University of Iowa, Iowa City 52242.) Journal of pharmaceutical sciences, (1993 Mar) 82 (3) 326-9. Journal code: 2985195R. ISSN: 0022-3549. Pub. country: United States. Language: English.

AB **Poly(D,L-lactide-co-glycolide**, 50:50) samples of similar molecular weight were obtained from three commercial sources and were characterized by gel permeation chromatography, differential scanning calorimetry, X-ray powder diffraction, viscometry, and proton nuclear magnetic resonance spectroscopy. Pellets were prepared by melt-pressing spray-dried polymer with a 4-mm standard concave punch and die set and a thermostated holder of original design. Amaranth (5% w/w) was incorporated in pellets used for release studies. Degradation and release studies were conducted at 37 degrees C in pH 7.2 phosphate buffered saline. The molecular weights of all polymers were found to decrease continuously after exposure to phosphate buffered saline. All polymers showed two distinct regions of molecular weight decrease. Mass loss experiments for all polymers resulted in sigmoidal curves typical of polymers undergoing bulk hydrolysis. The onset of mass loss (defined as 10% mass loss) was found to differ by as much as 6 days among the three polymers studied. The release studies showed an initial burst of release followed by a period of 15-25 days during which little or no dye was released. A second phase of release followed, lasting approximately 10 days, until all dye was released. The time at which release began slightly preceded the onset of mass loss.

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or park s?/au or kim w?/au)
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               OR CHO C?/AU OR PARK S?/AU OR KIM W?/AU)

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L12          2 L11 AND "POLY(L-LACTIDE-CO-GLYCOLIDE)"

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L13 ANSWER 1 OF 1 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN DUPLICATE 1
2002:842992 The Genuine Article (R) Number: 601GH. Preparation and
     characterization of pamidronate-loaded PLGA wafer for the treatment of
     bone resorption. Yoo J Y (Reprint); Kim S W; Khang G; Seong H S; Jeong J
     K; Kim H J; Lee J S; Lee H B. Chonbuk Natl Univ, Dept Adv Organ
     Mat Engn, 664-14 Dukjin, Chonju 561756, South Korea (Reprint); Chonbuk
     Natl Univ, Dept Adv Organ Mat Engn, Chonju 561756, South Korea; Chonbuk
     Natl Univ, Dept Polymer Sci & Technol, Chonju 561756, South Korea; Korea
     Res Inst Chem Technol, Biomat Lab, Taejon 305600, South Korea; Samchondang
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Pharm Co Ltd, Res Ctr, Seoul 105037, South Korea; Hanlim Univ, Coll Med, Dept Otorhinolaryngol, Anyang 431070, South Korea. POLYMER-KOREA (SEP 2002) Vol. 26, No. 5, pp. 680-690. Publisher: POLYMER SOC KOREA. ROOM 601, HATCHON BUILDING, 831 YEOKSAM-DONG, KANGNAM-KU, SEOUL 135-792, SOUTH KOREA . ISSN: 0379-153X. Pub. country: South Korea. Language: Korean. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Implantable biodegradable wafers were prepared with pamidronate-loaded **poly(L-lactide-Co-glycolide**) (PLGA. 75 : 25 mole ratio by lactide to glycolide. molecular weight 26000 and 90000 g/mole) by direct compression method for the sustained release of pamidronate to investigate the possibility for the treatment of bone resorption. Pamidronate-loaded PLGA powders were prepared by means of physical mixing and spray drying with the control of formulation factors and characterized by scanning electron microscope and X-ray diffractometer. The pamidronate-loaded PLGA powders fabricated into wafers by direct compression under the constant pressure and time at room temperature. These wafers were also observed for their structural characteristic, release pattern, and degradation pattern. The release rate of pamidronate increased with increasing their initial loading ratio as well as increasing wafer thickness. The molecular weight of PLGA affects the release pattern; the higher molecular weight of PLGA. the faster release rate. It can be explained that the higher viscosity of high molecular PLGA solution at same concentration tends to aggregate PLGA and pamidronate resulting in unstable pharmaceutical dosage form. This system had advantages in terms of simplicity in design and obviousness of drug release rate and may be useful as an implantable dosage form for the treatment of aural cholesteatoma.

=> s l11 and autoimmune disease
L14 328 L11 AND AUTOIMMUNE DISEASE

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L15 81 L14 AND ARTHRITIS

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L16 ANSWER 1 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
2004:162455 Document No. 140:198094 Pharmaceutical compositions comprising dehydroepiandrosterone or derivative for treating IL-1-related diseases. Seong, Sang-cheol; Lee, Myung-chul; Jo, Hyun-chul; **Park, Jung-sun** ; Jeong, Mi-young (S. Korea). U.S. Pat. Appl. Publ. US 2004038950 A1 20040226, 32 pp. (English). CODEN: USXXCO. APPLICATION: US 2003-358249 20030205. PRIORITY: KR 2002-50568 20020826.

AB The present invention relates to a pharmaceutical composition for treating (IL-1)-related disease or disorder, which comprises: (a) a therapeutically ED of dehydroepiandrosterone or its derivative The dehydroepiandrosterone and derivs. are antagonists of interleukin 1. The interleukin 1-related diseases include acute or chronic inflammation e.g. osteoarthritis, pancreatitis and asthma; **autoimmune disease** e.g. glomerular nephritis, rheumatoid **arthritis**, scleroderma and alphosis; infectious disease e.g. septicemia and septic shock.

L16 ANSWER 2 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2004118409 EMBASE Effector Function of Type II Collagen-Stimulated T Cells from Rheumatoid **Arthritis** Patients: Cross-Talk between T Cells and Synovial Fibroblasts. Cho M.-L.; Yoon C.-H.; Hwang S.-Y.; Park M.-K.; Min S.-Y.; Lee S.-H.; **Park S.-H.**; **Kim H.-Y.**. Dr. H.-Y. Kim, Kang-Nam St. Mary's Hospital, Department of Internal Medicine, Cathol. Univ. of Korea Sch. of Med., No. 505 Banpo-Dong, Seocho-Ku, Seoul

137-040, Korea, Republic of. rheuma@cmc.cuk.ac.kr. Arthritis and Rheumatism 50/3 (776-784) 2004.
Refs: 22.
ISSN: 0004-3591. CODEN: ARHEAW. Pub. Country: United States. Language: English. Summary Language: English.

AB Objective. To investigate the effector function exerted by type II collagen (CII)-stimulated T cells on rheumatoid **arthritis** (RA) fibroblast-like synoviocytes (FLS), and to determine their contribution to RA pathogenesis. Methods. We used enzyme-linked immunosorbent assays to measure the levels of interleukin-15 (IL-15), tumor necrosis factor a (TNFα), and IL-18 production by FLS that were cocultured with antigen-activated T cells. Likewise, we analyzed the levels of interferon-γ (IFNγ) and IL-17 production by RA T cells coincubated with FLS. To investigate the cross-talk between CII-stimulated T cells and RA FLS, we examined the effect of using a transwell membrane to separate T cells and FLS in a culture chamber, as well as the effect of adding an antibody to block CD40 ligation. Results. The levels of IL-15, TNFα, IFNγ, and IL-17 were all significantly increased in the serum of RA patients compared with normal control serum. Among the patients, the group with a stronger T cell proliferation response to CII showed higher levels of these inflammatory mediators. When coincubated with RA FLS, these T cells induced the production of IL-15, TNFα, and IL-18 by FLS with an intensity that increased in proportion to the duration of CII stimulation. T cells, in turn, responded to FLS stimulation by secreting higher amounts of IL-17 and IFNγ in coculture. Interestingly, T cells that were activated by CII for longer periods of time showed stronger induction of these cytokines. The cross-talk between T cells and FLS appeared to require direct cell-cell contact as well as CD40, ligation, at least in part. Conclusion. Through repeated stimulation by CII, RA synovial T cells became trained effector cells that induced the production of proinflammatory mediators by FLS, while in the process the T cells becoming more sensitized to the activation signal from FLS.

L16 ANSWER 3 OF 42 MEDLINE on STN DUPLICATE 1
2004136634. PubMed ID: 14978019. The point mutation of tyrosine 759 of the IL-6 family cytokine receptor gp130 synergizes with HTLV-1 pX in promoting rheumatoid **arthritis**-like **arthritis.** Ishihara Katsuhiko; Sawa Shin-Ichiro; Ikushima Hideto; Hirota Seiichi; Atsumi Toru; Kamimura Daisuke; **Park Sung-Joo**; Murakami Masaaki; Kitamura Yukihiko; Iwakura Yoichiro; Hirano Toshio. (Laboratory of Developmental Immunology, Graduate School of Frontier Biosciences, Osaka University, Suita, Osaka, Japan.) International immunology, (2004 Mar) 16 (3) 455-65. Journal code: 8916182. ISSN: 0953-8178. Pub. country: England: United Kingdom. Language: English.

AB Rheumatoid **arthritis** (RA) is a polygenic **autoimmune disease.** The autoimmunity develops from synergistic actions of genetic and environmental factors. We generated a double-mutant mouse by crossing two murine models of RA, a gp130 mutant knock-in mouse (gp130F759/F759) and an HTLV-1 pX transgenic mouse (pX-Tg), in a C57BL/6 background, which is resistant to **arthritis.** The mice spontaneously developed severe **arthritis** with a much earlier onset than the gp130F759/F759 mice and with a much higher incidence than did the pX-Tg mice. The symptoms of gp130F759/F759 mice, including lymphoadenopathy, splenomegaly, hyper-gamma-globulinemia, autoantibody production, increases in memory/activated T cells and granulocytes in the peripheral lymphoid organs, and a decrease in the class II MHC(bright) CD11c+ population, were augmented in the double mutants. Marked reductions in incidence, severity and immunological abnormalities were seen in the triple mutant, IL-6-/-/gp130F759/F759/pX-Tg, indicating that the **arthritis** in the double mutant is IL-6 dependent. gp130F759/F759/pX-Tg is a unique mouse model for RA.

L16 ANSWER 4 OF 42 MEDLINE on STN
2004243862. PubMed ID: 15142267. Induction of IL-10-producing CD4+CD25+ T

cells in animal model of collagen-induced **arthritis** by oral administration of type II collagen. Min So-Youn; Hwang Sue-Yun; Park Kyung-Su; Lee Jae-Sun; Lee Kang-Eun; Kim Kyung-Wun; Jung Young-Ok; Koh Hyunk-Jae; Do Ju-Ho; **Kim Haerim**; **Kim Ho-Youn.** (Rheumatism Research Center, Catholic Research Institute of Medical Science, The Catholic University of Korea, Seoul, Korea.. ho@catholic.ac.kr) . Arthritis research & therapy, (2004) 6 (3) R213-9. Journal code: 101154438. ISSN: 1478-6362. Pub. country: England: United Kingdom. Language: English.

AB Induction of oral tolerance has long been considered a promising approach to the treatment of chronic **autoimmune diseases**, including rheumatoid **arthritis** (RA). Oral administration of type II collagen (CII) has been proven to improve signs and symptoms in RA patients without troublesome toxicity. To investigate the mechanism of immune suppression mediated by orally administered antigen, we examined changes in serum IgG subtypes and T-cell proliferative responses to CII, and generation of IL-10-producing CD4+CD25+ T-cell subsets in an animal model of collagen-induced **arthritis** (CIA). We found that joint inflammation in CIA mice peaked at 5 weeks after primary immunization with CII, which was significantly less in mice tolerized by repeated oral feeding of CII before CIA induction. Mice that had been fed with CII also exhibited increased serum IgG1 and decreased serum IgG2a as compared with nontolerized CIA animals. The T-cell proliferative response to CII was suppressed in lymph nodes of tolerized mice also. Production of IL-10 and of transforming growth factor-beta from mononuclear lymphocytes was increased in the tolerized animals, and CD4+ T cells isolated from tolerized mice did not respond with induction of IFN-gamma when stimulated in vitro with CII. We also observed greater induction of IL-10-producing CD4+CD25+ subsets among CII-stimulated splenic T cells from tolerized mice. These data suggest that when these IL-10-producing CD4+CD25+ T cells encounter CII antigen in affected joints they become activated to exert an anti-inflammatory effect.

L16 ANSWER 5 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2004:124489 The Genuine Article (R) Number: 766HV. Identification of autoantibody against poly (ADP-ribose) polymerase (PARP) fragment as a serological marker in systemic lupus erythematosus. Jeoung D; Lim Y; Lee E B; Lee S; **Kim H Y**; Lee H; Song Y W (Reprint). Seoul Natl Univ, Coll Med, Clin Res Inst, Dept Internal Med, Med Res Ctr, Yongon Dong 28, Seoul 110744, South Korea (Reprint); Seoul Natl Univ, Coll Med, Clin Res Inst, Dept Internal Med, Med Res Ctr, Seoul 110744, South Korea; Kangweon Natl Univ, Div Life Sci, Chunchon 200701, South Korea; Seoul Natl Univ, Coll Med, Canc Genom Div, In2Gen Co, Canc Res Ctr, Seoul 110799, South Korea; Kyung Hee Univ, Grad Sch Biotechnol, Suwon, South Korea. JOURNAL OF AUTOIMMUNITY (FEB 2004) Vol. 22, No. 1, pp. 87-94. Publisher: ACADEMIC PRESS LTD ELSEVIER SCIENCE LTD. 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND. ISSN: 0896-8411. Pub. country: South Korea. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objectives: By utilizing serological analysis of a recombinant cDNA expression library (SEREX), we previously found that autoantibodies to poly (ADP-ribose) polymerase (PARP) are specifically present in the sera of patients with SLE. In this study, recombinant proteins of various domains of PARP were used to determine the PARP domain that is associated with SLE.

Methods: We produced four recombinant PARP proteins, which contained various PARP domains, and then carried out enzyme linked immunosorbent assay (ELISA) using these recombinant proteins to identify domains useful for SLE diagnosis. The recombinant proteins used in this analysis were; ADPNF (amino acids 1-234), ET-L2 (amino acids 339-680), ET-L3 (amino acids 681-1014), and ADPCF (amino acids 300-1014).

Result: ELISA with ADPNF or ET-L2 showed low sensitivity in the sera of patients with SLE (14.3% and 17.0% respectively), whereas ELISA with ET-L3 or ADPCF showed high sensitivity in the sera of patients with SLE (34.0% and 49.1%, respectively). Autoantibodies to ADPCF were not found in the sera of patients with rheumatoid **arthritis** (0/30), systemic

sclerosis (0/30) or healthy donors (0/54) and were rarely found in polymyositis/dermatomyositis (1/30) and Sjogren syndrome (1/14). Autoantibodies to ADPCF were closely associated with the presence of an oral ulcer in SLE (P=0.03, by the chi-square test).

Conclusion: The high sensitivity and specificity shown by autoantibodies to ADPCF protein could be used as a valuable serologic maker for the diagnosis of SLE.

L16 ANSWER 6 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2003:855905 Document No. 139:350938 Preparation of N-cinnamoyl-DOPA esters and related compounds as T lymphocyte inhibitors. Won, Jongwha; Lee, Keunhyeung; **Park, Seehyoung**; Kim, Sung-Joo; Yun, Su-Young; Kang, Mi-Ae; Hur, Yun-Gyoung; Youn, Jeehee; Yun, Yungdae; Park, Doohong; Oh, Jaetaek (Mogam Biotechnology Research Institute, S. Korea). PCT Int. Appl. WO 2003089405 A1 20031030, 109 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-KR751 20030414. PRIORITY: KR 2002-20481 20020415.

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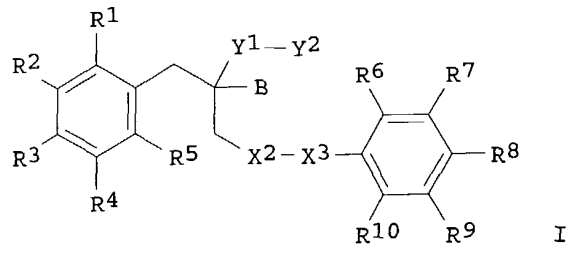

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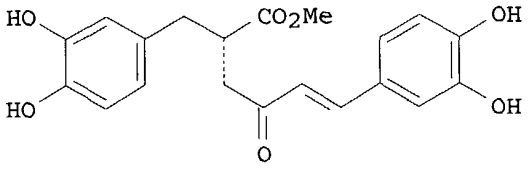

II

AB Title compds. I [R1-R10 = H, OH, halogen, alkoxy, CHO, CO2H, NH2, CF3, NO2, ≥ 1 of R1-R5 and R6-R10 = OH; X1 = O, S, NH, NMe, NEt, NHNH; X2 = CH2, CO, CS, CONH; X3 = bond, (un)substituted CH:CH, CH:CHCH:CH, CH2, CH2CH2; Y1 = H, CH2, CO, CS, alkyl, amino, 3-methyl-1,2,4-oxadiazol-5-yl, 3-benzyl-1,2,4-oxadiazol-5-yl; Y = absent, (un)substituted NH2, OH, SH; B = H, alkyl] were prepared as inhibitors of the activation of T lymphocytes by the src homol. region 2(SH2) domain of T lymphocyte (lck), useful for the treatment, prevention and/or diagnosis of graft rejection, **autoimmune diseases**, inflammatory diseases, etc. Thus, D-DOPA was converted to its Me ester and treated with caffeic acid to give the amide II which inhibited the binding of the lck SH2 domain with its cognate peptide < 10μM.

L16 ANSWER 7 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2003:396486 Document No. 138:400408 Humanized antibodies LB-00503 and LB-00506 specific for human 4-1BB and pharmaceutical compositions comprising said humanized antibodies. Hong, Hyo Jeong; **Park, Sung Sup**; Kang, Young Jun; Kang, Chang-Yuil; Yoon, Sung Kwan; Park, Youngwoo; Yoon, Hyesung; Jang, Hyunsook; Rha, Geun Bae; Yoo, Jin-San; Jeong, Jong Keun; Shim, Dong Sup; Park, Mijeong; **Kim, Hwadong**; **Park, Jung-gyu**; Yang, Jae-young (S. Korea). U.S. Pat. Appl. Publ. US 2003096976 A1 20030522, 34 pp., Cont.-in-part of U.S. 6,458,934. (English). CODEN: USXXCO. APPLICATION: US 2002-233996 20020904. PRIORITY: KR 1998-49177 19981117; KR 1999-16750 19990511; US 1999-438954 19991112.

AB The present invention relates to humanized monoclonal antibodies LB-00503 and LB-00506, which are specific for human 4-1BB mols., have high binding affinities and can bind efficiently with activated T cells expressing the 4-1BB mol., as well as pharmaceutical compns. Particularly, the present invention provides said humanized antibody LB-00503, which is modified from the humanized antibody Hz4B4-2 and substitutes the 61st amino acid, serine by asparagine in the amino acid residues of 59th61st and said humanized antibody LB-00506, which enhances the antibody binding affinity of said humanized antibody LB-00503 in which 2 amino acid residues of the right border in the antibody binding site CDR2 of the heavy chain variable region are substituted from glutamine→glycine (Q→G) to lysine→serine (K→S).

L16 ANSWER 8 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2003:1067203 The Genuine Article (R) Number: 750NM. Identification of auto-antibodies in the sera of patients with rheumatoid **arthritis*****. **Song Y W; Lee E B; Kim J; ***Kim H Y**; Jeoung D I (Reprint). Kangweon Natl Univ, Div Life Sci, Chunchon 200701, South Korea (Reprint); Seoul Natl Univ, Coll Med, Dept Internal Med, Clin Res Inst, Seoul 110799, South Korea; In2Gen Co, Canc Gen Div, Seoul 110799, South Korea; Kyung Hee Univ, Coll Life Sci, Suwon 442470, South Korea. BIOTECHNOLOGY LETTERS (DEC 2003) Vol. 25, No. 24, pp. 2049-2053. Publisher: KLUWER ACADEMIC PUBL. VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS. ISSN: 0141-5492. Pub. country: South Korea. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Serological analysis of a recombinant cDNA expression library was carried out and a number of auto-antibodies were found that were highly prevalent in the sera of such patients.

L16 ANSWER 9 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2003:886350 The Genuine Article (R) Number: 729WQ. Polymorphisms of IL-1B, IL-IRN, IL-2, IL-45 IL-6, IL-10, and IFN-gamma genes in the Korean population. Pyo C W; Hur S S; Kim Y K; Choi H B; Hong Y S; Kim D W; Kim C C; **Kim H K**; Kim T G (Reprint). Catholic Univ Korea, Coll Med, Dept Microbiol, Catholic Hemopoiet Stem Cell Bank, Seocho Ku, 505 Banpo Dong, Seoul 137701, South Korea (Reprint); Catholic Univ Korea, Coll Med, Dept Microbiol, Catholic Hemopoiet Stem Cell Bank, Seocho Ku, Seoul 137701, South Korea; Catholic Univ Korea, Coll Med, Dept Internal Med, Seoul 137701, South Korea; Catholic Univ Korea, Coll Med, Catholic Hemopoiet Stem Cell Transplantat Ctr, Seoul 137701, South Korea; Catholic Univ Korea, Coll Med, Dept Pediat, Seoul 137701, South Korea. HUMAN IMMUNOLOGY (OCT 2003) Vol. 64, No. 10, pp. 979-989. Publisher: ELSEVIER SCIENCE INC. 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA. ISSN: 0198-8859. Pub. country: South Korea. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cytokines play a crucial role in regulating the immune and inflammatory responses. The collective influence of several cytokines can regulate immune responses as complex as those underlying allograft rejections or **autoimmune diseases.** Polymorphisms in the regulatory regions of the cytokine genes may influence their expression. Therefore, the polymorphisms of cytokine genes are potentially important as genetic predictors of the disease susceptibility or clinical outcome. In 311 unrelated health Korean individuals, we investigated the polymorphisms of cytokine genes (interleukin-1 [IL-1], IL-2, IL-4, IL-6, IL-10, and

interferon-gamma [IFN-gamma]), which had been previously reported to be associated with a number of immune diseases, transplant complications, and direct or indirect influences on the level of expression and production. And we also compared the results to those published for other populations. The genotype distributions were consistent with the assumption of the Hardy-Weinberg equilibrium, with the exceptions of IL-1B +3954 and IL-6-174 polymorphisms. The polymorphisms examined in this study were almost similar to that observed in Asian populations. There were significant differences of the polymorphisms, except for IL-4 receptor alpha + 1902, between Korean and other populations. Comparing the alleles associated with higher level of expression and production, IL-1B +3954*T, IL-2-330*G, and IL-4-590*T alleles were significantly higher, and IL-1RN*A2, IL-10-1082*G, and IFN-gamma*2 alleles were lower in Koreans than other populations. Especially in IL-6 promoter -174 polymorphism, we found only the G allele associated with higher plasma IL-6 levels. In haplotype analysis of IL-10 promoter polymorphisms, the GCC haplotype, associated with higher expression of IL-10, was significantly lower in Koreans. These results may be helpful for understanding transplant-related complications, immune or **autoimmune diseases**, and malignant diseases in the Korean population. (C) American Society for Histocompatibility and Immunogenetics, 2003. Published by Elsevier Inc.

L16 ANSWER 10 OF 42 MEDLINE on STN DUPLICATE 2

2003280460. PubMed ID: 12808294. Oral administration of proteoglycan isolated from Phellinus linteus in the prevention and treatment of collagen-induced **arthritis** in mice. Kim Gi-Young; Kim Seung-Hoon; Hwang Sue-Yun; **Kim Ho-Youn**; Park Yeong-Min; **Park Soon-Kew**; Lee Min-Ki; Lee Sang-Hwa; Lee Tae-Ho; Lee Jae-Dong. (Department of Microbiology, College of Natural Sciences, Pusan National University, Pusan 609-735, South Korea.) Biological & pharmaceutical bulletin, (2003 Jun) 26 (6) 823-31. Journal code: 9311984. ISSN: 0918-6158. Pub. country: Japan. Language: English.

AB To examine whether oral administration of proteoglycan derived from Phellinus linteus, which is known as the medicinal mushroom, can prevent or treat collagen-induced **arthritis** (CIA) in mice as experimental model of **autoimmune disease.** CIA was induced by intradermal injection of type II collagen (CII) emulsified with complete freund's adjuvant (CFA) into the base of the tail (on day 7) followed by a booster injection on day 21 into the footpad. To examine the ability of proteoglycan to effect the inhibition of CIA, doses of proteoglycan were orally administered on day 0 (pre-administration) or day 28 (post-administration) at two groups. The inhibition of CIA by oral administration of proteoglycan was associated with decrease in anti-CII IgG and IgG2a antibodies (Abs) as well as varying kinds of cytokines including IL-12, TNF-alpha, and IFN-gamma. The results showed that administration of proteoglycan was followed by decrease of CIA of the mice in pre- and post-administration groups. Our findings suggest that immunomodulating proteoglycan isolated from P. linteus may be crucially involved in the prevention and treatment of autoimmune joint inflammation such as rheumatoid **arthritis**, although no definite role of anti-CII Abs in the human disease has been established.

L16 ANSWER 11 OF 42 EMBASE on STN

2003293113 EMBASE Thyrotropin-mediated repression of class II trans-activator expression in thyroid cells: Involvement of STAT3 and suppressor of cytokine signaling. **Kim H.**; Suh J.M.; Hwang E.S.; Kim D.W.; Chung H.K.; Song J.H.; Hwang J.H.; Park K.C.; Ro H.K.; Jo E.-K.; Chang J.-S.; Lee T.-H.; Lee M.-S.; Kohn L.D.; Shong M.. Dr. M. Shong, Laboratory of Endocrine Cell Biology, Department of Internal Medicine, Chungnam Natl. Univ. Sch. of Med., 640 Daesadong, Chungku, Taejon 301-721, Korea, Republic of. minhos@cnu.ac.kr. Journal of Immunology 171/2 (616-627) 15 Jul 2003.
Refs: 56.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language:

English. Summary Language: English.

AB It has been suggested that class I and class II MHC are contributing factors for numerous diseases including autoimmune thyroid diseases, type 1 diabetes, rheumatoid **arthritis**, Alzheimer's disease, and multiple sclerosis. The class II trans-activator (CIITA), which is a non-DNA-binding regulator of class II MHC transcription, regulates the constitutive and inducible expression of the class I and class II genes. FRTL-5 thyroid cells incubated in the presence of IFN-γ have a significantly higher level of cell surface rat MHC class II RTI.B. However, the IFN-γ-induced RT1.B expression was suppressed significantly in cells incubated in the presence of thyrotropin. Thyrotropin (TSH) represses IFN-γ-induced CIITA expression by inhibiting type IV CIITA promoter activity through the suppression of STAT1 activation and IFN regulatory factor 1 induction. This study found that TSH induces transcriptional activation of the STAT3 gene through the phosphorylation of STAT3 and CREB activation. TSH induces SOCS-1 and SOCS-3, and TSH-mediated SOCS-3 induction was dependent on STAT3. The cell line stably expressing the wild-type STAT3 showed a higher CIITA induction in response to IFN-γ and also exhibited TSH repression of the IFN-γ-mediated induction of CIITA. However, TSH repression of the IFN-γ-induced CIITA expression was not observed in FRTL-5 thyroid cells, which stably expresses the dominant negative forms of STAT3, STAT3-Y705F, and STAT3-S727A. This report suggests that TSH is also engaged in immunomodulation through signal cross-talk with the cytokines in thyroid cells.

L16 ANSWER 12 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3

2003438240 EMBASE Diagnostic significance of antibodies to heat shock proteins. **Kim H.**. H. Kim, Department of Pharmacology, Brain Korea 21 Proj. for Med. Sci., Yonsei Univ. College of Medicine, Seoul 120-752, Korea, Republic of. kim626@yumc.yonsei.ac.kr. Clinica Chimica Acta 337/1-2 (1-10) 2003.
Refs: 123.
ISSN: 0009-8981. CODEN: CCATAR. Pub. Country: Netherlands. Language: English.

L16 ANSWER 13 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2002:793602 Document No. 137:294952 Preparation of 3-cyclopentyloxy-4-methoxyphenyl benzoisothiazolinones as tumor necrosis factor-α (TNF-α) or cAMP phosphodiesterase IV (PDE 4) inhibitors. **Park, Joon-Seok**; Byun, Young-Seok; Moon, Seong-Cheol (Daewoong Pharmaceutical Co., Ltd., S. Korea). PCT Int. Appl. WO 2002081447 A1 20021017, 36 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.
APPLICATION: WO 2001-KR579 20010406.

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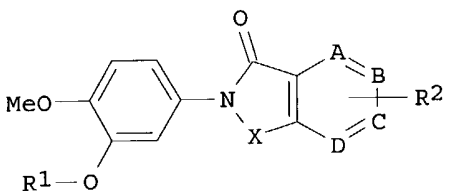

I

AB The title compds. [I; R1 = alkyl, cycloalkyl, arylalkyl, etc.; R2 = H, halo, OH, etc.; X = O, C, CO, S, etc.; A, B, C, D = C, N, N-oxide] having the activity to inhibit tumor necrosis factor-α (TNF-α) or cAMP phosphodiesterase IV (PDE 4), and therefore possessing important biol. therapeutic effect on inflammatory and **autoimmune diseases** associated with a detrimental excess of TNF-α, were prepared and formulated. Thus, reacting 6-(aminomethyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-isoindolinone with 1-oxo-1H-1λ4-benzo[1,2]dithiol-3-one (prepns. given) in CH_2Cl_2 afforded 76% I [R1 = cyclopentyl; R2 = H; X = S; A-D = C] which showed 68.5% inhibition of TNF-α synthesis in vitro.

L16 ANSWER 14 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2002:793601 Document No. 137:310811 Preparation of 2-(3-cyclopentyloxy-4-methoxyphenyl)isoindolinones as tumor necrosis factor-α (TNF-α) or cAMP phosphodiesterase IV (PDE 4) inhibitors. **Park, Joon-Seok**; Byun, Young-Seok (Daewoong Pharmaceutical Co., Ltd., S. Korea). PCT Int. Appl. WO 2002081446 A1 20021017, 62 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-KR578 20010406.

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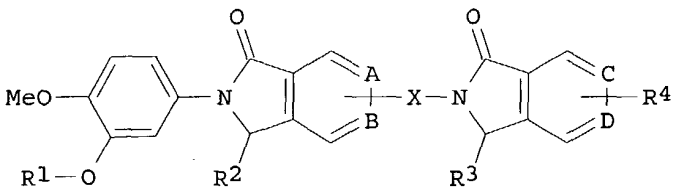

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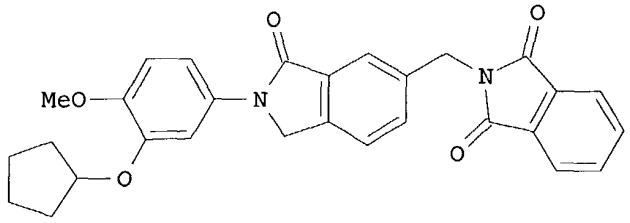

II

AB The title compds. [I; R1 = alkyl, cycloalkyl, arylalkyl, etc.; R2, R3 = H, OH, O, etc.; R4 = H, halo, OH, etc.; X = O, C, CO, NH, CONH; A, B, C, D = C, N, N-oxide] possessing important biol. therapeutic effect on inflammatory and **autoimmune diseases** associated with a detrimental excess of TNF-α, were prepared and formulated. Thus, reacting 2-(3-cyclopentyloxy-4-methoxyphenyl)-6-(hydroxymethyl)-1-isoindolinone (preparation given) and phthalimide in the presence of triphenylphosphine and di-Et azodicarboxylate in THF afforded 85% II which showed 79.3% inhibition of TNFα synthesis in vitro.

L16 ANSWER 15 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2002:658153 Document No. 137:197337 Cloning, characterization and therapeutic use of a human TRAF6-inhibiting protein. Lee, Zang-Hee; **Kim, Hong-Hee** (Komed Co., Ltd., S. Korea). PCT Int. Appl. WO 2002066508 A1 20020829, 99 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-KR276 20020221. PRIORITY: KR 2001-8595 20010221.

AB The present invention is based on the identification, recombinant production and characterization of a novel human tumor necrosis factor receptor associated factor 6 (TRAF6)-inhibiting protein. The cDNA sequence and the encoded amino acid sequence of the human TRAF6-inhibiting protein are disclosed. The proteins contain a KRAB domain at their N-termini and 14 C2H2 type zinc finger motifs at their C-termini, bind to TFAF6 but do not bind to TRAF2 and TRAF3, and inhibit activities of NF-κB or AP-1 in a signal transduction pathway of tumor necrosis factor (TNF) by interacting with TRAF6. Cloning of the TRAF6-inhibiting protein, a method for screening a substance capable of modulating activity of TRAF6-inhibiting proteins, and a pharmaceutical composition useful in treating and preventing diseases associated with hyper- or hypoactivity of TRAF6, NF-κB or AP-1 are provided.

L16 ANSWER 16 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2002:122959 Document No. 136:183715 Preparation of quinoline derivatives as antiinflammatory agents. Broka, Chris Allen; **Kim, Woongki**; McLaren, Kevin Lee; Smith, David Bernard (F. Hoffmann-La Roche A.-G., Switz.). PCT Int. Appl. WO 2002012192 A1 20020214, 69 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP8880 20010801. PRIORITY: US 2000-PV224196 20000809.

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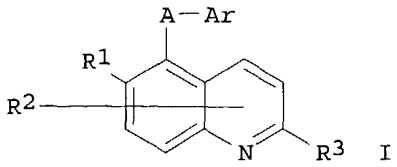


I

AB The title compds. I [A = S, etc.; Ar = (un)substituted phenyl; R1 = H, alkoxy, etc.; R2 = H, alkyl, etc.; R3 = SO2R12, etc.; R12 = alkyl, etc.] are prepared I are useful as inhibitors of COX-II and, therefore, may be used for the treatment of a disease treatable by administration of a selective COX-II inhibitor, such as an inflammatory disease, **autoimmune disease.** Processes for preparing I are claimed. 5-(2,4-Difluorophenylsulfanyl)-2-methanesulfonyl-6-methoxyquinoline in vitro showed IC50 values of >40 μM and <0.2 μM against COX-I and COX-II, resp. Formulations are given.

L16 ANSWER 17 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2002:748809 Document No. 137:277793 Humanized antibody specific for human

4-1BB. Hong, Hyo Jeong; **Park, Sung Sup**; Kang, Young Jun; Kang, Chang-yuil; Yoon, Sung Kwan (Lg Chemical Ltd., S. Korea). U.S. US 6458934 B1 20021001, 31 pp. (English). CODEN: USXXAM. APPLICATION: US 1999-438954 19991112. PRIORITY: KR 1998-19177 19981117; KR 1999-16750 19990511.

AB The present invention is directed to humanized antibodies that specifically bind the protein 4-1BB. The antibodies can be made by grafting of the complementarity determining regions (CDR's) of mouse monoclonal antibody to human 4-1BB to the remaining portions of a human antibody and by making further amino acid replacements. In addition, a pharmaceutical composition that includes the humanized antibody can be made and can be used to treat **autoimmune diseases** to suppress an immune response. The humanized antibody of the invention has high affinity for human 4-1BB, and exhibits sequence similarity to human antibody. As a result, the pharmaceutical composition of the present invention can be used to treat **autoimmune disease** and act as an immunosuppressant in humans without much side-effect.

L16 ANSWER 18 OF 42 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2002:370536 Document No.: PREV200200370536. Identification of p7F, a bioflavonoid from natural product and analysis of its anti-inflammatory effects. Lee, HeeGu [Reprint author]; **Kim, HyoSun** [Reprint author]; Yu, KyungAe [Reprint author]; Choe, YongKyung [Reprint author]; Lim, Jong-Seok [Reprint author]; Yoon, Do-Young [Reprint author]. Cell Biol Lab, KRIBB, Yuseong, P. O. Box 115, Taejon, ChungNam, 303-333, South Korea. FASEB Journal, (March 22, 2002) Vol. 16, No. 5, pp. A1054. print. Meeting Info.: Annual Meeting of Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002. CODEN: FAJOEC. ISSN: 0892-6638. Language: English.

AB Inflammation is complex series of vascular, leukocyte, and plasma-interactive events of the immune responses that occur in response to injury. The immune response is regulated by a highly complexed and intricate network of control elements. A dynamic and ever-shifting balance exists between pro-inflammatory cytokines and anti-inflammatory components of the human immune system. The regulation of inflammation by these cytokines and cytokine inhibitors is complicated by the fact that the immune system has redundant pathways with multiple elements having similar physiologic effects. In this study, we isolated and identified the anti-inflammatory molecule, tetramethoxyflavone (p7F) from Artemisia absinthium and investigated their ability to inhibit the inflammatory responses. p7F inhibited the following effects: 1) IL-1-induced proliferation of Th2 cells, 2) TNF-a-induced expressions of ICAM-1, COX-2 and iNOS. However, anti-inflammatory cytokine IL-4 and IL-10 were up-regulated. Thus, these inhibitors can be clinically applied in the treatment of **autoimmune diseases** such as rheumatoid **arthritis.**

L16 ANSWER 19 OF 42 MEDLINE on STN DUPLICATE 4
2002623658. PubMed ID: 12370259. A point mutation of Tyr-759 in interleukin 6 family cytokine receptor subunit gp130 causes autoimmune **arthritis.** Atsumi Toru; Ishihara Katsuhiko; Kamimura Daisuke; Ikushima Hideto; Ohtani Takuya; Hirota Seiichi; Kobayashi Hideyuki; **Park Sung-Joo**; Saeki Yukihiko; Kitamura Yukihiko; Hirano Toshio. (Department of Molecular Oncology (C7), Graduate School of Medicine, Osaka University, Suita, Japan.) Journal of experimental medicine, (2002 Oct 7) 196 (7) 979-90. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB We generated a mouse line in which the src homology 2 domain-bearing protein tyrosine phosphatase (SHP)-2 binding site of gp130, tyrosine 759, was mutated to phenylalanine (gp130(F759/F759)). The gp130(F759/F759) mice developed rheumatoid **arthritis** (RA)-like joint disease. The disease was accompanied by autoantibody production and accumulated memory/activated T cells and myeloid cells. Before the disease onset, the T cells were hyperresponsive and thymic selection and peripheral clonal deletion were impaired. The inhibitory effect of IL-6 on Fas ligand

expression during activation-induced cell death (AICD) was augmented in gp130(F759/F759) T cells in a manner dependent on the tyrosine residues of gp130 required for signal transducer and activator of transcription 3 activation. Finally, we showed that disease development was dependent on lymphocytes. These results provide evidence that a point mutation of a cytokine receptor has the potential to induce **autoimmune disease.**

L16 ANSWER 20 OF 42 MEDLINE on STN DUPLICATE 5
2002497835. PubMed ID: 12358851. Allelic frequency of the MCP-1 promoter -2518 polymorphism in the Korean population and in Korean patients with rheumatoid **arthritis**, systemic lupus erythematosus and adult-onset Still's disease. Hwang S-Y; Cho M-L; Park B; Kim J-Y; Kim Y-H; Min D-J; Min J-K; **Kim H-Y.** (Institute of Immunobiology, Catholic Institutes of Medical Science, The Catholic University of Korea, Seoul, Korea.. dutuya@cmc.cuk.ac.kr) . European journal of immunogenetics : official journal of the British Society for Histocompatibility and Immunogenetics, (2002 Oct) 29 (5) 413-6. Journal code: 9106962. ISSN: 0960-7420. Pub. country: England: United Kingdom. Language: English.
AB The frequency of the monocyte chemoattractant protein-1 (MCP-1) -2518 G-type polymorphism in Koreans is significantly higher than the frequencies reported for Caucasians and Afro-Americans. The G- vs. A-allele profile in patients with systemic **autoimmune diseases** is similar to that in healthy Koreans, and does not appear to contribute to elevated MCP-1 production in patients.

L16 ANSWER 21 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:723853 The Genuine Article (R) Number: 587NJ. Metallothionein suppresses collagen-induced **arthritis** via induction of TGF-beta and down-regulation of proinflammatory mediators. Youn J; Hwang S H; **Ryoo Z Y**; Lynes M A; Paik D J; Chung H S; **Kim H Y (Reprint).** Catholic Univ Korea, Catholic Res Inst Med Sci, 505 Banpodong Seocho Ku, Seoul 137040, South Korea (Reprint); Catholic Univ Korea, Catholic Res Inst Med Sci, Seoul 137040, South Korea; Hanyang Univ, Coll Med, Inst Biomed Sci, Seoul 133791, South Korea; Hanyang Univ, Coll Med, Dept Anat & Cell Biol, Seoul 133791, South Korea; Univ Connecticut, Dept Mol & Cell Biol, Storrs, CT 06269 USA. CLINICAL AND EXPERIMENTAL IMMUNOLOGY (AUG 2002) Vol. 129, No. 2, pp. 232-239. Publisher: BLACKWELL PUBLISHING LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0009-9104. Pub. country: South Korea; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Metallothionein is a low molecular weight, cysteine-rich, stress response protein that can act as an antioxidant and as an immunosuppressive agent in instances of antigen-dependent adaptive immunity. In this context, we assessed the therapeutic potential and mechanisms of action of metallothionein in a collagen-induced **arthritis** model. Repeated administration of metallothionein-I + II during the course of disease dramatically reduced the incidence and severity of the disease. Joint tissues isolated from boostered paws of metallothionein-I + II-treated mice expressed significantly reduced levels of proinflammatory mediators, such as tumour necrosis factor (TNF)-alpha and cyclooxygenase-2, when compared with those of control-treated mice. Lymph node cells obtained from metallothionein-I + II -injected mice exhibited a significant decrease in the proliferative response and a remarkable increase in tumour growth factor (TGF)-beta production in response to type II collagen. Taken together, these results suggest that metallothionein-I + II promote the development of type II collagen-specific, TGF-beta-producing cells to antagonize the expansion of arthritogenic cells. This could lead to local suppression of inflammatory responses by inhibiting the expression of proinflammatory molecules. Thus, this study demonstrates the suppressive effects of metallothionein on collagen-induced **arthritis**, and indicates that there may be a potential therapeutic application for manipulation of metallothionein during the treatment of autoimmune disorders.

L16 ANSWER 22 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
2002:813789 Document No. 138:280734 3D QSAR (COMFA) of a series of potent and highly selective VLA-4 antagonists. Singh, Juswinder; Van Vlijmen, Herman; **Lee, Wen-Cherng**; Liao, Yusheng; Lin, Ko-Chung; Ateeq, Humayun; Cuervo, Julio; Zimmerman, Craig; Hammond, Charles; Karpusas, Michael; Palmer, Rex; Chattopadhyay, Tapan; Adams, Steven P. (Biogen Inc, Cambridge, MA, 02142, USA). Journal of Computer-Aided Molecular Design, 16(3), 201-211 (English) 2002. CODEN: JCADEQ. ISSN: 0920-654X. Publisher: Kluwer Academic Publishers.

AB The integrin VLA-4 ($\alpha 4\beta 1$) is involved in the migration of white blood cells to sites of inflammation, and is implicated in the pathol. of a variety of diseases including asthma and multiple sclerosis. We report the structure-activity relationships of a series of VLA-4 antagonists that were based upon the integrin-binding sequence of the connecting segment peptide of fibronectin (Leu-Asp-Val), and of VCAM-1 (Ile-Asp-Ser), both natural ligands of VLA-4. We explore variation in the ligand derived peptide portion of these antagonists and also in the novel N-terminal cap, which have discovered through chemical optimization, and which confers high affinity and selectivity. Using the x-ray derived conformation of the Ile-Asp-Ser region of VCAM-1, we rationalize the structure-activity relationships of these antagonists using 3D QSAR (COMFA). The COMFA model was found to be highly predictive with a cross-validated RCV2 of 0.7 and a PRESS of 0.49. The robustness of the model was confirmed by testing the influence of various parameters, including grid size, column filtering, as well as the role of orientation of the aligned mols. Our results suggest that the VCAM-1 structure is useful in generating highly predictive models of our VLA-4 antagonists. The COMFA model coupled with the knowledge that the peptide amides are tolerant to methylation should prove useful in future peptidomimetic design studies.

L16 ANSWER 23 OF 42 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2002:501268 Document No.: PREV200200501268. A new concept of B-cell activation in **autoimmune diseases**: The accumulative and maturative type of B-cell activation in synovitis. Krenn, V. [Reprint author]; Magalhaes, R.; **Kim, H.-J.**; Moeller, J.; Berek, C.. Institut fuer Pathologie, Universitaetsklinikum der Humboldt-Universitaet, Berlin, Germany. Pathology Research and Practice, (2002) Vol. 198, No. 3, pp. 160. print.
Meeting Info.: 86th Meeting of the German Society of Pathology. Vienna, Austria. April 03-06, 2002.
CODEN: PARPDS. ISSN: 0344-0338. Language: English.

L16 ANSWER 24 OF 42 MEDLINE on STN DUPLICATE 6
2002341496. PubMed ID: 12083777. Identification of autoantibodies associated with systemic lupus erythematosus. Lim Yoon; Lee Dae-Yeon; Lee Seongeun; **Park Sae-Young**; Kim Jongwan; Cho Bomsoo; Lee Hosoon; **Kim Hae-Yeong**; Lee Eunbong; Song Yeong Wook; Jeoung Doo-Il. (Cancer Genomics Division, In2Gen Company, 6th Floor, Cancer Research Center, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-799, Republic of Korea.) Biochemical and biophysical research communications, (2002 Jul 5) 295 (1) 119-24. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Systemic lupus erythematosus (SLE) is an **autoimmune disease** characterized by the presence of antinuclear antibodies. We performed serological analysis of cDNA expression library (SEREX) to identify autoantibodies associated with SLE. The screening of three different cDNA expression libraries with pooled sera of patients with SLE yielded 11 independent clones that reacted with pooled sera of patients with SLE. In this screening, autoantibodies to poly(ADP-ribose) polymerase (PARP), U1snRNP, and galectin-3 were prevalent in the sera of patients with SLE (26/68, 25/68, 12/63, respectively). The frequency of autoantibody to PARP was significantly higher in SLE than that of healthy donors (0/76) (38.2% vs 0%, $p<0.00001$). The autoantibody to PARP was infrequently detected in the serum of patients with RA (1/50). However,

autoantibody to PARP was not found in the sera of patients with other rheumatic diseases including Sjogren's syndrome (0/19), systemic sclerosis (0/18), and polymyositis/myositis (0/37). The frequency of autoantibody to human galectin-3 (12/63) was significantly higher in SLE than that of healthy donors (0/56) (19% vs 0%, p=0.0006). Autoantibody to galectin-3 was not found in the sera of patients with rheumatoid **arthritis** (0/50), Sjogren's syndrome (0/18), and systemic sclerosis (0/19). Interestingly, autoantibody to galectin-3 was also prevalent in the sera of patients with polymyositis/dermatomyositis (16/37, 43.2%). Further functional characterization of these autoantibodies would be necessary to determine their value as diagnostic markers or to define clinical subsets of patients with SLE. Statistical analysis revealed that the presence of autoantibody to PARP was inversely related with pleurisy, and the presence of autoantibody to galectin-3 related with renal disease.

L16 ANSWER 25 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
2001:137052 Document No. 134:183507 Immunological tolerance-induction agent. **Kim, Ho-Youn; Park, Jong-Sang; Ryoo, Zae-Young ; Bae, Euiyoung; Lee, Woo-Kyoung; Cho, Chul-Soo; Park, Sung-Hwan; Kim, Wan-Uk** (S. Korea). PCT Int. Appl. WO 2001012222 A1 20010222, 50 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-KR460 19990818.

AB A method for treating **autoimmune diseases** by administering orally to a mammal suffering from **autoimmune diseases** particles of biodegradable polymers or their complexes with an autoimmune antigen is provided. Only single administration can effectively induce oral tolerance to **autoimmune diseases** , resulting in a strong and prolonged suppression of the diseases.

L16 ANSWER 26 OF 42 MEDLINE on STN DUPLICATE 7
2001372866. PubMed ID: 11429548. TACI-ligand interactions are required for T cell activation and collagen-induced **arthritis** in mice. Wang H; Marsters S A; Baker T; Chan B; **Lee W P**; Fu L; Tumas D; Yan M; Dixit V M; Ashkenazi A; Grewal I S. (Department of Immunology, Genentech Inc. South San Francisco, CA 94080, USA.) Nature immunology, (2001 Jul) 2 (7) 632-7. Journal code: 100941354. ISSN: 1529-2908. Pub. country: United States. Language: English.

AB Interactions of the tumor necrosis factor superfamily members B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) with their receptors-transmembrane activator and CAML interactor (TACI) and B cell maturation molecule (BCMA)-on B cells play an important role in the humoral immune response. Whereas BCMA is restricted to B cells, TACI is also expressed on activated T cells; we show here that TACI-Fc blocks the activation of T cells in vitro and inhibits antigen-specific T cell activation and priming in vivo. In a mouse model for rheumatoid **arthritis** (RA), an **autoimmune disease** that involves both B and T cell components, TACI-Fc treatment substantially inhibited inflammation, bone and cartilage destruction and disease development. Thus, BLyS and/or APRIL are important not only for B cell function but for T cell-mediated immune responses. Inhibition of these ligands might have therapeutic benefits for **autoimmune diseases**, such as RA, that involve both B and T cells.

L16 ANSWER 27 OF 42 MEDLINE on STN DUPLICATE 8
2001555900. PubMed ID: 11602650. Prodigiosin blocks T cell activation by inhibiting interleukin-2Ralpha expression and delays progression of autoimmune diabetes and collagen-induced **arthritis.** Han S B;

Park S H; Jeon Y J; Kim Y K; **Kim H M**; Yang K H.
(Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Yusong, Taejon, Korea.) Journal of pharmacology and experimental therapeutics, (2001 Nov) 299 (2) 415-25. Journal code: 0376362. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB Prodigiosin (PDG) was previously reported to be a T cell-specific immunosuppressant. Here we describe the mechanism of action of PDG in T cells and the effect of PDG on **autoimmune diseases.**
PDG selectively suppresses concanavalin A (Con A)-induced T cell proliferation, but has little effect on lipopolysaccharide-induced proliferation of B cells and nitric oxide production of macrophages. Although PDG does not block interleukin (IL)-2 production, it efficiently inhibits interleukin-2 receptor alpha-chain (IL-2Ralpha) expression, and this results in a disruption of the IL-2/IL-2R signaling pathway, on which a great part of the regulation of T cell activation depends. PDG blocks T cell differentiation into effector helper T cells secreting interferon-gamma and IL-4 as well as into effector cytotoxic T lymphocytes expressing perforin, which is at least in part resulting from inhibition of the IL-2/IL-2R signaling. PDG indirectly blocks signal transducer and activator of transcription activation by inhibiting cytokine signalings in Con A-activated T cells, although it does not inhibit the activation of nuclear factor-kappaB, nuclear factor of activated T cells, and activator protein-1. As direct evidence of immunosuppression in vivo, we show that PDG markedly reduced blood glucose levels and cellular infiltration into the pancreatic islets in nonobese diabetic mice, and that it also delays the onset of collagen-induced **arthritis** in DBA/1 mice. In conclusion, our results demonstrate that PDG has a unique mode of action, namely, that it blocks T cell activation by inhibiting primarily IL-2Ralpha expression in the IL-2/IL-2R signaling, and show that this compound represents a promising immunosuppressant candidate for the treatment of **autoimmune diseases.**

L16 ANSWER 28 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:539496 The Genuine Article (R) Number: 448XM. Experimental autoimmune myocarditis in A/J mice is an interleukin-4-dependent disease with a Th2 phenotype. Afanasyeva M; Wang Y; Kaya Z; **Park S**; Zilliox M J; Schofield B H; Hill S L; Rose N R (Reprint). Johns Hopkins Univ, Dept Pathol, Ross Bldg, Room 659, 720 Rutland Ave, Baltimore, MD 21205 USA (Reprint); Johns Hopkins Med Inst, Dept Pathol, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Mol Microbiol & Immunol, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Environm Hlth Sci, Baltimore, MD 21205 USA. AMERICAN JOURNAL OF PATHOLOGY (JUL 2001) Vol. 159, No. 1, pp. 193-203 . Publisher: AMER SOC INVESTIGATIVE PATHOLOGY, INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3993 USA. ISSN: 0002-9440. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Myocarditis in humans is often associated with an autoimmune process in which cardiac myosin (CM) is a major autoantigen. Experimental autoimmune myocarditis (EAM) is induced in mice by immunization with CM. We found that EAM in A/J mice exhibits a Th2-like phenotype demonstrated by the histological picture of the heart lesions (eosinophils and giant cells) and by the humoral response (association of IgG1 response with disease and up-regulation of total IgE). Blocking interleukin (IL)-4 with anti-IL-4 monoclonal antibody (mAb) reduced the severity of EAM. This reduction in severity was associated with a shift from a Th2-like to a Th1-like phenotype represented by a reduction in CM-specific IgG1; an increase in CM-specific IgG2a; an abrogation of total IgE response; a decrease in IL-4, IL-5, and IL-13; as well as a dramatic increase in interferon (IFN)-gamma production in vitro. Based on the latter finding, we hypothesized that IFN-gamma limits disease. Indeed, IFN-gamma blockade with a mAb exacerbated disease. The ameliorating effect of IL-4: blockade was abrogated by co-administration of anti-IFN-gamma mAb. Thus, EAM represents a model of an organ-specific **autoimmune disease** associated with a Th2 phenotype, in which IL-4 promotes the disease and IFN-gamma limits it. Suppression of IFN-gamma represents

at least one of the mechanisms by which IL-4 promotes EAM.

L16 ANSWER 29 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
2000:351560 Document No. 133:3714 Humanized antibody specific for human 4-1bb and pharmaceutical composition comprising same. Hong, Hyo Jeong; **Park, Sung Sup**; Kang, Young Jun; Kang, Chang Yuil; Yoon, Sung Kwan (LG Chemical Limited, S. Korea). PCT Int. Appl. WO 2000029445 A1 20000525, 83 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-KR689 19991117. PRIORITY: KR 1998-49177 19981117; KR 1999-16750 19990511.

AB The present invention is directed to humanized antibodies that specifically bind the protein 4-1BB. The antibodies can be made by grafting of the complementarity determining regions (CDR's) of mouse monoclonal antibody to human 4-1BB to the remaining portions of a human antibody and by making further amino acid replacements. In addition, a pharmaceutical composition that includes the humanized antibody can be made and can be used to treat **autoimmune diseases** to suppress an immune response. The humanized antibody of the invention has high affinity for human 4-1BB, and exhibits sequence similarity to human antibody. As a result, the pharmaceutical composition of the present invention can be used to treat **autoimmune disease** and act as an immunosuppressant in humans without much side-effect.

L16 ANSWER 30 OF 42 MEDLINE on STN DUPLICATE 9
2001090240. PubMed ID: 10963123. Histopathology and molecular pathology of synovial B-lymphocytes in rheumatoid **arthritis.** Krenn V; Souto-Carneiro M M; **Kim H J**; Berek C; Starostik P; Konig A; Harms H; Muller-Hermelink H K. (Institute for Pathology, University of Wurzburg, Germany.. path119@mail.uni-wuerzburg.de) . Histology and histopathology, (2000 Jul) 15 (3) 791-8. Ref: 42. Journal code: 8609357. ISSN: 0213-3911. Pub. country: Spain. Language: English.

AB B-cells of the rheumatoid synovial tissue are a constant part of and, in some histopathological subtypes, the dominant population of the inflammatory infiltrate, located in the region of tissue destruction. The pattern of B-cell distribution and the relationship to the corresponding antigen-presenting cells (follicular dendritic reticulum cells: FDCs) show a great variety. B-cells may exhibit (i) a follicular organization forming secondary follicles; (ii) follicle-like patterns with irregularly formed FDC networks, and (iii) a diffuse pattern of isolated FDCs. Molecular analysis of immunoglobulin VH and VL genes from human synovial B-cell hybridomas and synovial tissue demonstrates somatic mutations due to antigen activation. The FDC formations in the synovial tissue may therefore serve as an environment for B-cell maturation, which is involved in the generation of autoantibodies. An autoantibody is defined as "pathogenic" if it fulfills the Witebsky-Rose-Koch criteria for classical **autoimmune diseases**: definition of the autoantibody; induction of the disease by transfer of the autoantibody; and isolation of the autoantibody from the disease-specific lesion. B-cells from rheumatoid synovial tissue show specificity for FcIgG, type II collagen, COMP, sDNA, tetanus toxoid, mitochondrial antigens (M2), filaggrin and bacterial HSPs. The contributions of these antigens to the pathogenesis of RA are still hypothetical. A possible contribution could derive from crossreactivity and epitope mimicry: due to crossreaction, an antibody directed originally against a foreign infectious agent could react with epitopes from articular tissues, perpetuating the local inflammatory process. The characteristic distribution pattern, the localisation within the area of tissue destruction, the hypermutated IgVH and IgVL genes, and their exclusive function to recognize conformation-dependent antigens suggest a central role for B-cells in the inflammatory process of

rheumatoid **arthritis.** Therefore, the analysis of synovial B-cell hybridomas and experimental expression of synovial IgVH and IgVL genes will help to characterise the antigens responsible for the pathogenesis of rheumatoid **arthritis.**

L16 ANSWER 31 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:898698 The Genuine Article (R) Number: 376AF. A humanized anti-4-1BB monoclonal antibody suppresses antigen-induced humoral immune response in nonhuman primates. Hong H J; Lee J W; **Park S S**; Kang Y J; Chang S Y; Kim K M; Kim J O; Murthy K K; Payne J S; Yoon S K; Park M J; Kim I C; Kim J G; Kang C Y (Reprint). SEOUL NATL UNIV, COLL PHARM, IMMUNOL LAB, KWANAK GU, SHILLIM DONG, SEOUL 151742, SOUTH KOREA (Reprint); SEOUL NATL UNIV, COLL PHARM, IMMUNOL LAB, KWANAK GU, SEOUL 151742, SOUTH KOREA; SEOUL NATL UNIV, COLL MED, SEOUL 151742, SOUTH KOREA; KOREA RES INST BIOSCI & BIOTECHNOL, TAEJON, SOUTH KOREA; SW FDN BIOMED RES, SAN ANTONIO, TX 78284; LG CHEM LTD, BIOTECH RES INST, TAEJON, SOUTH KOREA. JOURNAL OF IMMUNOTHERAPY (NOV-DEC 2000) Vol. 23, No. 6, pp. 613-621. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621. ISSN: 1053-8550. Pub. country: SOUTH KOREA; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The interaction of 4-1BB and its ligand plays an important role in the regulation of T-cell-mediated immune responses. In this study, the authors examined the effect of a humanized anti-4-1BB monoclonal antibody (H4B4) on ovalbumin-induced immune responses in baboons. Previously, a mouse monoclonal antibody, 4B4 against the human 4-1BB molecule, was generated and characterized. Based on this antibody, a humanized version of 4B4 monoclonal antibody was constructed and the resultant antibody, H4B4, showed full recovery of the binding activity of the original antibody 4B4: a 1.5-fold increase in affinity for 4-1BB. In addition, H4B4 mediated antibody-dependent cellular cytotoxicity of activated human peripheral blood T cells and CEM cells in a dose-dependent manner. Weekly administration of H4B4 at doses of 1 or 4 mg/kg could suppress immunoglobulin G production against ovalbumin. This: was not a result of the overall immune suppression, because the numbers of B and T cells and the total immunoglobulin G production were not altered during treatment with H4B4. These findings suggest that treatment with H4B4 may be a valid therapeutic approach to control unwanted immune responses in persons with **autoimmune diseases.**

L16 ANSWER 32 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:122358 The Genuine Article (R) Number: 281QQ. Divergent effect of cyclosporine on Th1/Th2 type cytokines in patients with severe, refractory rheumatoid **arthritis.** **Kim W U**; Cho M L; Kim S I; Yoo W H; Lee S S; Joo Y S; Min J K; Hong Y S; Lee S H; **Park S H**; **Cho C S**; **Kim H Y (Reprint).** CATHOLIC UNIV KOREA, KANG NAM ST MARYS HOSP, SCH MED, RES CTR CATHOLIC MED CTR, 505 BANPO DONG, SEOUL 137040, SOUTH KOREA (Reprint); CATHOLIC UNIV KOREA, KANG NAM ST MARYS HOSP, SCH MED, RES CTR CATHOLIC MED CTR, SEOUL 137040, SOUTH KOREA. JOURNAL OF RHEUMATOLOGY (FEB 2000) Vol. 27, No. 2, pp. 324-331. Publisher: J RHEUMATOL PUBL CO. 920 YONGE ST, SUITE 115, TORONTO ON M4W 3C7, CANADA. ISSN: 0315-162X. Pub. country: SOUTH KOREA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective, To investigate the effect of cyclosporine on cytokine production, especially on T helper 1 (Th1) and T helper 2 (Th2) type cytokines, in patients with rheumatoid **arthritis** (RA).

Methods. A 16 week randomized, double blind, placebo controlled study of cyclosporine (2.5 to 4 mg/kg/day) was conducted in 40 patients with severe, refractory RA who had residual inflammation and disability despite partial responses to prior maximal tolerated dose of methotrexate (MTX; < 15 mg/week) and low dose prednisone (< 10 mg/day). Clinical and laboratory variables, and circulating levels of interleukin 2 (IL-2), IL-4, IL-10, IL-12, tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma) measured by ELISA were compared between patients (cyclosporine group) treated with cyclosporine plus MTX and those (placebo group) treated with placebo plus MTX at entry and at 16 weeks.

Results. At 16 weeks, the cyclosporine group (n = 17), compared with the placebo group (n = 17), had greater decreases in tender joints, swollen joints, patient global assessment, patient self-assessed disability, and C-reactive protein, as well as having more patients with > 20% improvement. Comparison of circulating cytokines at entry and at 16 weeks showed significant decreases of IL-2. (median -61 vs 7 pg/ml; p = 0.004) (''+'' denotes increase, ''-'' denotes decrease), IL-12 (median -313 vs -14 pg/ml; p = 0.002), TNF-alpha (median -55 vs 5 pg/ml; p < 0.001), and IFN-gamma (median -21 vs 5 pg/ml; p = 0.003), and a significant increase of IL-10 (median 55 vs -12 pg/ml; p < 0.001) in the cyclosporine group compared with the placebo group. The degree of IL-10 increases correlated strongly with the degree of IL-12 decreases in the cyclosporine group (r = 0.572, p = 0.016). However, there was no change in circulating IL-4 between the 2 groups. Within the cyclosporine group, the improved patients (n = 10) compared to the non-improved patients (n = 7) had a greater increase in circulating IL-10 (median 172.0 vs 85.2%; p = 0.01). The rate of increase of IL-10 strongly correlated with the rate of improvement of joint scores (r = 0.718, p = 0.001) after administration of cyclosporine.

Conclusion. Our results suggest that the therapeutic effect of cyclosporine is achieved by correcting a Th1/Th2 imbalance (a shift of Th1 type to Th2 type), which may be involved in the pathogenesis of RA; and that circulating IL-IO is useful to assess the clinical improvements in patients with RA after administration of cyclosporine.

L16 ANSWER 33 OF 42 MEDLINE on STN DUPLICATE 10
2000477472. PubMed ID: 11028842. Suppression of collagen-induced **arthritis** with histone H1. Jung N; Kim D S; Kwon H Y; Yi Y W; Kim D; Kang A D; **Cho C H**; Hong S S; Lee H S; Bae I. (Therapeutic Gene Group, Samyang Genex Biotech Res. Inst., Taejeon, Korea.) Scandinavian journal of rheumatology, (2000) 29 (4) 222-5. Journal code: 0321213. ISSN: 0300-9742. Pub. country: Norway. Language: English.

AB Besides roles in nucleus mediating the condensation of DNA into chromatin, the involvement of histones in **autoimmune diseases**, hormone regulation, and killing leukemia cells has been reported. In order to investigate the functions of histones on an **autoimmune disease**, histone H1 was injected into collagen-induced **arthritis** (CIA) mice. A dramatic suppression of CIA by histone H1 was observed at a dose of 1 mg/kg bodyweight of mouse. In addition, the increased level of anti-inflammatory cytokine IL-10 was detected in cultured splenocytes from the mouse treated with histone H1. These findings suggest that histone H1 suppresses the collagen-induced **arthritis**, possibly by increasing the level of IL-10 production.

L16 ANSWER 34 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
2000:671934 Document No. 134:212539 Suppression of collagen induced **arthritis** (CIA) by single administration of poly(lactic-coglycolic acid) (PLGA) entrapping CII. **Lee, W. K.**; **Bae, E. Y.**; **Kim, W. U.**; **Kim, H. Y.**; **Park, J. S.** (Department of Chemistry, Seoul National University, Seoul, 151-742, S. Korea). Proceedings of the International Symposium on Controlled Release of Bioactive Materials, 27th, 213-214 (English) 2000. CODEN: PCRMEY. ISSN: 1022-0178. Publisher: Controlled Release Society, Inc..

AB Orally administered self-antigens suppress autoimmunity in animal models, including exptl. allergic encephalomyelitis (EAE), collagen-induced **arthritis** (CIA), uveitis, and diabetes in the non-obese diabetic mouse. Rheumatoid **arthritis** (RA) is a representative **autoimmune disease**, characterized by destructive polyarthritis. Type II collagen (CII) is a strong candidate for putative autoantigen of RA. Antigen-specific immune suppression using CII has been tested in RA. Biodegradable particles such as poly(lactic-coglycolic acid) have been studied as a drug carrier system, because of their advantages such as enhanced absorption, biocompatibility, and sustained drug release. A study was conducted which showed that singly administered biodegradable particles entrapping CII could suppress **arthritis**

more effectively than in the case of repeated administration of CII only.

L16 ANSWER 35 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:45178 The Genuine Article (R) Number: 271ZG. The role of IL-12 in inflammatory activity of patients with rheumatoid **arthritis** (RA) . **Kim W U**; Min S Y; Cho M L; Youn J; Min J K; Lee S H; **Park S H**; **Cho C S**; **Kim H Y (Reprint)**. CATHOLIC UNIV KOREA, KANG NAM ST MARYS HOSP, CTR RHEUMAT DIS, CATHOLIC RES INST MED SCI, SEOUL 137040, SOUTH KOREA (Reprint); CATHOLIC UNIV KOREA, KANG NAM ST MARYS HOSP, CTR RHEUMAT DIS, CATHOLIC RES INST MED SCI, SEOUL 137040, SOUTH KOREA. CLINICAL AND EXPERIMENTAL IMMUNOLOGY (JAN 2000) Vol. 119, No. 1, pp. 175-181. Publisher: BLACKWELL SCIENCE LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0009-9104. Pub. country: SOUTH KOREA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The aim of this study was to investigate the role of IL-12 in patients with RA. IL-12 (p70) and its associated cytokines were measured in sera and synovial fluid (SF) using an enzyme-linked immunosorbent method. Seven American College of Rheumatology (ACR) core set measures as well as IL-12 levels were sequentially monitored at the commencement and 4 months after treatment with a low-dose steroid and disease-modifying anti-rheumatic drugs (DMARDs). In sera, 64 (42.2%) of 152 RA patients had detectable concentrations of IL-12 (p70), whereas one (1.4%) of 69 osteoarthritis (OA) patients and five (10%) of 50 healthy controls had detectable IL-12 ($P < 0.001$). The median level of circulating IL-12 was also higher in RA patients ($P < 0.001$). In SF, the number of patients with detectable IL-12 and the median IL-12 levels were significantly higher in RA patients ($n = 53$) than in OA patients ($n = 22$). In paired samples ($n = 53$) of sera and SF from RA patients, IL-12 levels were higher in the SF than in sera ($P < 0.001$). Patients with detectable IL-12 ($n = 51$) in sera had higher tender joint scores ($P = 0.003$), swollen joint scores ($P < 0.001$) and C-reactive protein (CRP; $P = 0.036$), than those without ($n = 55$). Four months after treatment with DMARDs, the improved group showed a larger IL-12 decrease than the non-improved group ($P = 0.017$). The levels of IL-12 correlated positively with those of IL-2, interferon-gamma, IL-6, and tumour necrosis factor-alpha, but were correlated inversely with those of IL-10. Our results demonstrate that IL-12 levels reflect RA disease activity and that IL-12 is involved in the production of proinflammatory cytokines. An IL-12 blockade could be useful for the treatment of RA.

L16 ANSWER 36 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:463991 The Genuine Article (R) Number: 204VU. Genetic risk and protective factors for idiopathic inflammatory myopathy in Koreans and American whites - A tale of two loci. Rider L G (Reprint); Shamim E; Okada S; Pandey J P; Targoff I N; OHanlon T P; **Kim H A**; Lim Y S; Han H; Song Y W; Miller F W. US FDA, LAB MOL & DEV IMMUNOL, CTR BIOL EVALUAT & RES, BLDG 29B, ROOM 2G11, HFM-561, BETHESDA, MD 20892 (Reprint); US FDA, CTR FOOD SAFETY & APPL NUTR, WASHINGTON, DC 20204; UNIV OKLAHOMA, MED SCI CTR, VET AFFAIRS MED CTR, OKLAHOMA CITY, OK; OKLAHOMA MED RES FDN, OKLAHOMA CITY, OK 73104; SEOUL NATL UNIV HOSP, SEOUL 110744, SOUTH KOREA; CATHOLIC UNIV, COLL MED, SEOUL, SOUTH KOREA. ARTHRITIS AND RHEUMATISM (JUN 1999) Vol. 42, No. 6, pp. 1285-1290. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106. ISSN: 0004-3591. Pub. country: USA; SOUTH KOREA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective, To better understand genetic contributions to autoimmunity, immunogenetic markers were studied in two racially discrete and geographically isolated populations of patients with idiopathic inflammatory myopathy (IIM),

Methods, Clinical characteristics, as well as clinical and autoantibody subsets, were defined in 151 American white patients and 50 Korean patients with IIM, HLA-DRB1 and DQA1 genotyping was performed on patients and racially matched controls by standard molecular techniques. Gm allotypes and phenotypes were determined by the hemagglutination-inhibition method,

Results. HLA-DRB1*0301, the linked allele DQA1*0501, and DRB1 alleles sharing the first hypervariable region motif (EYSTS13)-E-9 were major genetic risk factors for the development of myositis in whites (corrected P [P-corr] < 0.0004, odds ratio [OR] 11.2, 4.5, and 3.1, respectively, for each factor versus controls). Although both the white and Korean patients had a similar distribution of clinical characteristics, autoantibody profiles, and clinical groups, no HLA-DRB1 nor DQA1 allele or motif was found to be a risk factor for IIM in the Korean patients. However, DRB1*14 was a protective factor in Korean patients without myositis-specific autoantibodies (P-corr = 0.004, OR 0.046), In addition, although no Gm phenotype or allotype was identified as a risk factor in whites, Gm 21 was a protective factor for the development of IIM in Koreans (P-corr = 0.024, OR 0.3),

Conclusion. Although myositis patients in the US and Korea share similar clinical and serologic features, the immune response genes predisposing to and protecting from myositis in each of these ethnic groups differ at two chromosomal loci. These data suggest that multiple genetic loci should be studied to identify risk and protective factors for some **autoimmune diseases** in various ethnic populations.

on STN DUPLICATE 11

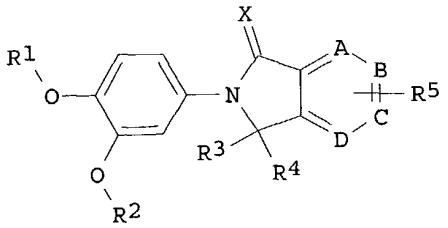
1999105327 EMBASE Newly synthesized phosphodiesterase 4 (PDE4) inhibitor, DWP205505, inhibits TNF-α secretion and mRNA expression. Lee S.K.; Lee S.-A.; Byun H.; Cho M.-L.; **Kim W.-U.**; **Park S.-H.**; **Cho C.-S.**; Joo Y.-S.; Lee S.-S.; Yoo E.-S.; Ho Jung Son; **Kim H.-Y.**. S.K. Lee, Research Institute of Immunobiology, Catholic Res. Inst. of Med. Sci., Catholic University of Korea, Seoul 157-701, Korea, Republic of. sukklee@cmc.cuk.ac.kr. Journal of Microbiology and Biotechnology 9/1 (106-112) 1999.
Refs: 23.
ISSN: 1017-7825. CODEN: JOMBES. Pub. Country: Korea, Republic of.
Language: English. Summary Language: English.

AB The therapeutic potential of phosphodiesterase 4 (PDE4) inhibitors in inflammatory diseases including some **autoimmune diseases** has been explored recently with some hopeful results. These PDE4 inhibitors are thought to show their anti-inflammatory effect by down-regulating tumor necrosis factor-α (TNF-α) production in lymphocytes and macrophages. A high concentration of TNF-α has been found in rheumatoid **arthritis** (RA) synovium and reducing TNF-α using biological agents was proven to be an effective RA treatment. To test the possibility of using PDFA inhibitors for RA treatment, the effects of a newly synthesized PDE4 inhibitor, DWP205505, on TNF-α and IL-10 production was tested in cells isolated from normal peripheral blood and rheumatoid **arthritis** synovial fluid. Cytokine production was assayed at the protein level by sandwich enzyme-linked immunosorbent assay (ELISA) and at the mRNA expression level by semi-quantitative RT-PCR. Another PDE4 inhibitor, RP73401, was used for comparison. DWP205505 and RP73401 had no harmful effect on cell viability up to 10 μM concentration during the 24 h culture period. DWP205505 as well as RP73401 significantly reduced TNF-α secretion from lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMC) and synovial fluid mononuclear cells (SFMC). The effect of DWP205505 or RP73401 treatment on the mRNA expression of TNF-α was also studied in LPS-stimulated PBMC and SFMC. TNF-α mRNA expression was increased by LPS stimulation and both of the PDE4 inhibitors suppressed TNF- α mRNA expression. For interleukin-10 (IL-10), a little different results were obtained from PBMC and SFMC; IL-10 secretion was unaffected by LPS stimulation and only minimally affected by both of the PDE4 inhibitors in PBMC. In unstimulated SFMC, DWP205505 and RP73401 slightly enhanced IL-10 secretion, while they reduced IL-10 secretion from LPS-stimulated SFMC where IL-10 secretion was a lot higher than unstimulated SFMC. These results suggest that the newly synthesized PDE4 inhibitor DWP205505 may have anti- rheumatoid **arthritis**

activity.

L16 ANSWER 38 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
1998:682069 Document No. 129:275840 Preparation of novel 3,4-dialkoxyphenylisoindolinones and -pyrrolopyridines as tumor necrosis factor-α (TNF-α) inhibitors. Baik, Kyong-Up; Yoo, Eun-Sook; Byun, Young-Seok; Lee, Seck-Jong; Jang, Byung-Soo; Son, Ho-Jun; Lee, Jae-Ho; Cho, Jae-Youl; Lee, Se-Jong; Chang, Woo-Ik; Lee, June-goo; **Park, Ji-soo**; Lee, Byung-goo; **Park, Joon-seck**; Moon, Seong-cheol; Park, Myung-hwan (Daewoong Pharmaceutical Co., Ltd., S. Korea). PCT Int. Appl. WO 9842666 A1 19981001, 88 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-KR48 19980317. PRIORITY: KR 1997-9706 19970321.

GI



I

AB The title compds. [I; X = O, S; A, B, C, D = C, N, N-oxide; R1 = lower alkyl; R2 = lower alkyl, cycloalkyl, hydroxycycloalkyl, etc.; R3 = H, OH; R4 = H, halo, N3, etc.; R5 = H, halo, OH, etc.], having the activity to inhibit tumor necrosis factor-α (TNF-α), and therefore useful in the treatment of inflammatory disease, **autoimmune disease**, **arthritis**, asthma, type I diabetes mellitus, etc., were prepared and formulated. Thus, reaction of 2-(3-cyclopentyloxy-4-methoxyphenyl)isoindolin-1,3-dione (preparation described) with MeMgBr in THf followed by treatment of a solution of the resulting 3-methyl-3-hydroxy-2-(3-cyclopentyloxy-4-methoxyphenyl)isoindolin-1-one in CH2Cl2 with Et3SiH and F3CCO2H afforded I [X = O; A-D = C; R1 = Me; R2 = cyclopentyl; R3 = H; R4 = Me; R5 = H] which showed 90% inhibitory activity against TNF-α synthesis in vitro.

L16 ANSWER 39 OF 42 MEDLINE on STN DUPLICATE 12
97383370. PubMed ID: 9237933. B-cell activation and development within chronically inflamed synovium in rheumatoid and reactive **arthritis**. Berek C; **Kim H J.** (Deutsches Rheuma ForschungsZentrum, Berlin Monbijoustr. 2, Berlin, 10117, Germany.) Seminars in immunology, (1997 Aug) 9 (4) 261-8. Ref: 38. Journal code: 9009458. ISSN: 1044-5323. Pub. country: United States. Language: English.

AB In **autoimmune diseases**, B cells often accumulate in the affected tissue. In patients with rheumatoid **arthritis** or reactive **arthritis**, germinal center-like structures may develop in the inflamed synovial tissue. B cells from these structures were isolated and their V-gene repertoire determined. The majority of synovial B cells are long-term memory cells and thus are part of the chronic inflammatory reaction. In the synovium a micro-environment is built up which allows the activation of naive and memory B cells and the diversification of their V-gene repertoire. The analysis of plasma cells suggests that these cells are long lived and hence accumulate in the synovial tissue under chronic activation.

L16 ANSWER 40 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
97:693098 The Genuine Article (R) Number: XV908. In vivo the environmental pollutants lead and mercury induce oligoclonal T cell responses skewed toward type-2 reactivities. Heo Y; **Lee W T**; Lawrence D A (Reprint). NEW YORK STATE DEPT HLTH, WADSWORTH CTR LABS & RES, POB 509, ALBANY, NY 12201 (Reprint); NEW YORK STATE DEPT HLTH, WADSWORTH CTR LABS & RES, ALBANY, NY 12201; SUNY ALBANY, SCH PUBL HLTH, ALBANY, NY 12201. CELLULAR IMMUNOLOGY (1 AUG 1997) Vol. 179, No. 2, pp. 185-195. Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0008-8749. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB An oligoclonal utilization of V beta s has been reported for pathogenesis of several **autoimmune diseases**, antitumorigenic activity, and superantigen-regulation of thymic T cell development. Altered ratios of Th1 and Th2 cells also are observed in immunodysregulations, leading to impaired cell-mediated immunity with an increased incidence of infectious disease or cancer and/or aberrant immunity that could culminate with an **autoimmune disease** . Lead (Pb) and mercury (Hg) are known pollutants with immunodisrupting activities; Hg is known to cause autoimmune glomerulonephritis. Both metals are known to suppress host resistance to pathogens. To further evaluate the manner by which these metals cause in vivo immunomodulation, their in vivo effects on V beta expression were evaluated along with the Th1 and Th2 frequency. Exposure of BALB/c mice to PbCl2 or HgCl2 induced an oligoclonal response with increases of V beta 5(+), V beta 7(+), and V beta 13(+) CD4(+) splenic, but not thymic, T cells. A significantly skewed frequency of Pb-induced splenic Th2 cells expressing VP 7 or VP 13 over Th1 cells was determined by Limiting dilution analysis, but this Th2 predominance was not observed with CD4(+) T cells expressing V beta 8. DO11.10 transgenic mouse exposed to Pb and antigen also demonstrated a skewed type-a response evidenced by significantly increased IgE levels, lowered IFN-gamma levels, and increased IgG1 and lowered IgG2a anti-OVA levels. Even in the absence of specific T cell specificity in the transgenic mouse antigen, due to the restricted T cell specificity in the transgenic mouse model, Pb still was able to skew the response toward type-a reactivity. However, this skewing occurred only in the presence of antigen. Therefore, the Pb-induced oligoclonal T cell response in BALB/c mice which must be initiated by self-antigens and was predominately type-a may be responsible for autoantibody production and the detrimental health effects associated with Pb exposure. (C) 1997 Academic Press.

L16 ANSWER 41 OF 42 MEDLINE on STN DUPLICATE 13
97012872. PubMed ID: 9157091. Three HLA-DMB variants in Korean patients with **autoimmune diseases.** Kim T G; Carrington M; Choi H B; **Kim H Y**; Han H. (Department of Microbiology and Immunology, Catholic University Medical College, Seoul, Korea.) Human immunology, (1996 Mar) 46 (1) 58-60. Journal code: 8010936. ISSN: 0198-8859. Pub. country: United States. Language: English.

L16 ANSWER 42 OF 42 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1992:326884 Document No.: PREV199294028725; BA94:28725. INTERLEUKIN-6 ACTIVITY OF SYNOVIAL FLUID AND SERUM IN RHEUMATOID **ARTHRITIS.** CHO S G [Reprint author]; **KIM H Y.** DEP INTERNAL MED, CATHOLIC UNIV MED COLLEGE, SEOUL, KOREA. Journal of Catholic Medical College, (1992) Vol. 45, No. 1, pp. 115-122.
CODEN: KTUNAA. ISSN: 0368-7015. Language: KOREAN.

AB Interleukin-6(IL-6), previously known as B cell stimulatory factor 2(BSF-2) is a multifunctional cytokine that is produced by a various cells and plays an important role in the host defense mechanism such as regulation of immune response, acute phase reaction and hematopoiesis. Recent investigations have demonstrated that unregulated expression of IL-6 gene and overproduction of IL-6 were involved in the pathogenesis of cardiac myxoma, Castleman's disease, **autoimmune disease** , proliferative glomerulonephritis and certain lymphoid malignancies,

especially plasmacytoma/multiple myeloma. We tried to evaluate the regulatory effect of IL-6 on the pathogenesis of rheumatoid **arthritis** (RA) which is characterized by hyperactivation of B cells, presence of various autoantibodies and increase in acute phase proteins and platelets. The IL-6 activity was measured by bioassay using the murine IL-6 dependent hybridoma cell lines (MH60, BSF2) and ELISA method. The results were as follows; 1. IL-6 activity was significantly elevated in synovial fluid and serum from patients with rheumatoid **arthritis** (RA, n = 25) as compared with non-RA group (n = 10) including osteoarthritis (n = 6) and seroenegative spondyloarthritides (n = 4) ($P < 0.001$). 2. Positive correlations between IL-6 activity and C-reactive proteins in serum were observed in patients with RA ($r=0.752$). 3. There was no significant differences between bioassay and ELISA method. The results suggest that unregulated production of IL-6 may play an important role in the pathogenesis of RA and could explain local as well as generalized symptoms of RA. However, it is not known whether excessive production of IL-6 is a primary event in the disease process, or secondary consequence.

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=> s polylactides
L17         720 POLYLACTIDES

=> s l17 and autoimmune
L18           0 L17 AND AUTOIMMUNE

=> s l17 and arthritis
L19           3 L17 AND ARTHRITIS

=> dup remove l19
PROCESSING COMPLETED FOR L19
L20           3 DUP REMOVE L19 (0 DUPLICATES REMOVED)

=> d l20 1-3 cbib abs

L20  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2004 ACS on STN
2003:491015  Document No. 139:57936  Solid pharmaceutical for parenteral
     administration. Hansen, Henrik Egesborg; Sabra, Mads Christian;
     Rasmussen, Thomas Buch (Novo Nordisk A/S, Den.).  PCT Int. Appl. WO
     2003051328 A1 20030626, 51 pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT,
     AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM,
     DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
     KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
     MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN,
     TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ,
     MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES,
     FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG,
     TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2002-DK865 20021217.
     PRIORITY: DK 2001-1901 20011218.
AB   A solid pharmaceutical composition for parenteral administration comprises an
     inner matrix containing at least 1 therapeutic agent, and a biodegradable, and
     water-impermeable coating covering part of the surface of the composition,
     wherein the inner matrix disintegrates upon contact with animal tissue or
     tissue fluids. The coating is made from a material selected from the
     group consisting of polyesters such as polyglycolides,
     polylactides and polylactic polyglycolic acid copolymers, etc.
     The inner-matrix may comprise a binder, e.g., mannitol, and the active
     agent may comprise insulin. Dry amorphous Maltidex H16323 (35 g) was
     mixed with 35 g human insulin. The mixture was cooled and investigated
     under a microscope and there was no air entrapment, which also is
     indicated by the constant torque. The insulin activity before mixing was
     99.62% and after mixing 97.52%.

L20  ANSWER 2 OF 3  EMBASE  COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on STN
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2000066396 EMBASE IARC monographs programme on the evaluation of carcinogenic risks to humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 74/- (9-376) 1999.
ISSN: 0250-9555. CODEN: IMCHE5. Pub. Country: France. Language: English. Summary Language: English.
AB 6.1 Exposure data: A wide range of metals and their alloys, polymers, ceramics and composites are used in surgically implanted medical devices and prostheses and dental materials. Most implanted devices are constructed of more than one kind of material (implants of complex composition). Since the early 1900s, metal alloys have been developed for these applications to provide improved physical and chemical properties, such as strength, durability and corrosion resistance. Major classes of metals used in medical devices and dental materials include stainless steels, cobalt-chromium alloys and titanium (as alloys and unalloyed). In addition, dental casting alloys are based on precious metals (gold, platinum, palladium or silver), nickel and copper and may in some cases contain smaller amounts of many other elements, added to improve the alloys' properties. Orthopaedic applications of metal alloys include arthroplasty, osteosynthesis and in spinal and maxillofacial devices. Metallic alloys are also used for components of prosthetic heart valve replacements, and pacemaker casings and leads. Small metallic parts may be used in a wide range of other implants, including skin and wound staples, vascular endoprostheses, filters and occluders. Dental applications of metals and alloys include fillings, prosthetic devices (crowns, bridges, removable prostheses), dental implants and orthodontic appliances. Polymers of many types are used in implanted medical devices and dental materials. Illustrative examples are silicones (breast prostheses, pacemaker leads), polyurethanes (pacemaker components), polymethacrylates (dental prostheses, bone cements), poly(ethylene terephthalate) (vascular grafts, heart valve sewing rings, sutures), polypropylene (sutures), polyethylene (prosthetic joint components), polytetrafluoroethylene (vascular prostheses), polyamides (sutures) and **polylactides** and poly(glycolic acids) (bioresorbables). Ceramic materials based on metal oxides (alumina, zirconia) find use in joint replacements and dental prostheses. Other materials based on calcium phosphate are used as bone fillers and implant coatings. Pyrolytic carbon applications include heart valves and coatings for implants. Composites are used mainly in dental fillings. Although precise numbers are not available, many millions of people worldwide have implanted devices, which may remain in place for years. Foreign bodies, such as bullets and pellets from firearms and metallic fragments from explosions, may penetrate and remain in human tissues for long periods of time. Internal exposure to constituents, including lead (from bullets and pellets) and depleted uranium (from shell and missile fragments), may result. 6.2 Human carcinogenicity data: Sixteen case reports have described neoplasms originating from bone or soft connective tissue in the region of metal implants. An analytical study did not report an increased risk for soft-tissue sarcoma after metal implants. No association with dental amalgam was found in a case-control study in Australia. The 30 case reports of breast cancer following silicone implants for cosmetic breast augmentation appear unlikely to correspond to an excess of breast cancer. All five cohort studies involving a total of more than 18 000 women treated with surgical prostheses made of silicone (or polyurethane-coated silicone) for cosmetic breast augmentation conducted in Canada, Denmark, Sweden and the United States consistently found no evidence of increased risk of breast cancer. The combined results of the four largest cohort studies show a 25% reduction in risk. Similar results were reported by a large case-control study including more than 2000 cases and 2000 controls in the United States. All cohort studies were based on subjects exposed to implanted silicone at an early age, usually between the ages of 30 and 40 years, so that the number of breast cancer cases observed in each study was relatively small. Except for the case-control study in the United States, only limited allowance was made for potential confounding factors, although no clear evidence has emerged as to the relevance of any such factor to a possible association between implanted silicone and breast

cancer risk. Three of the studies considered the issue of latency, with observation periods of up to 10 years or more, but even in the group of women with follow-up of 10 years or more, there was no suggestion of increased risk. The risk of cancer following surgical implantation of silicone prostheses for breast reconstruction after breast cancer was considered in a study in France. The results of this study suggest no excess risk of second primary breast or other cancer, distant metastases, local recurrence or death from breast cancer. The reduced risks for breast cancer found in the cohort and case- control studies are unlikely to be due to chance, and no bias that would explain these findings has been identified. Four cohort studies of women with surgical breast implants in Denmark, Sweden and the United States reported on cancers at sites other than the breast. None of these studies found an increased risk for all cancers combined. Two studies reported increased risk for lung cancer, but these results were based on a total of only nine observed cases. For no other cancer site was there consistent evidence of an increased risk, although the statistical power to detect an increased risk of rare neoplasms, including soft-tissue sarcomas, was small. Out of the large number of patients with orthopaedic implants of complex composition (metal with bone cement with or without polyethylene), a total of 35 cases have been reported of malignant neoplasms arising from the bone or the soft tissue in the region of an implant. Fourteen cohort studies of patients following total knee or total hip replacement from six countries were performed to investigate cancer incidence in these populations. Two of the studies from Finland and two studies from Sweden were partially overlapping. One study included only patients with metal-on-metal implants, five studies included only patients with polyethylene-on-metal implants, while the remaining studies included patients with mixed or unspecified types of implant. One study showed a small increase in overall cancer incidence, while the remaining studies showed overall decreases. Four of these studies suggested an excess risk for specific cancers, including Hodgkin's disease, non-Hodgkin lymphoma, leukaemia and kidney cancer. However, results of the other studies were not consistent with this observation. In one small cohort study from Denmark of patients with a finger or hand implant, an increased risk of lymphohaematopoietic cancer was observed. Additionally, two case-control studies, one including cases with soft-tissue sarcoma and the other including lymphoma and leukaemia, were carried out in the United States. The latter overlaps with one of the cohort studies. Neither of these studies showed an association with the presence of implants of complex composition. Most of the studies did not have information on possible confounding variables such as immunosuppressive therapy or rheumatoid **arthritis** for the lymphomas and analgesic drugs for kidney cancer. The follow-up in most of the studies may have been too short to evaluate cancer occurring many years after exposure; in some studies with longer follow-up, the numbers of long-term survivors were low. Thirteen cases of breast cancer and one case of plasmacytoma have been reported in patients with cardiac pacemakers. Ten cases of different neoplasms have been reported at the site of non-metallic foreign bodies. Eight cases of sarcoma have been reported at the site of vascular grafts. No conclusions can be drawn from these case reports. Twenty-three cases of sarcomas, twenty-three cases of carcinomas and seven cases of brain tumours have been reported at the site of metallic foreign bodies, mainly bullets and shrapnel fragments. 6.3 Veterinary studies: Despite the large number and variety of both metallic and non-metallic internal fixation devices used in dogs in recent decades, only about 60 cases of sarcomas, primarily of bone, have been reported. In addition, four cases of sarcomas at the site of other foreign bodies have been reported in dogs. One case-control study found no association between metallic implants used to stabilize fractures in dogs and the development of bone or soft-tissue tumours. In contrast, at least 563 cases of vaccine-associated sarcomas in cats have been reported in just six years, with an estimated annual incidence of 1-13 per 10 000 vaccinated cats. Vaccine-associated sarcomas have been mostly associated with administration of recently introduced feline vaccines containing adjuvant. Tumours that develop at vaccination sites are morphologically different

from those that develop at non-vaccination sites. A cohort study found that cats developed sarcomas in a shorter time at sites used for vaccination than at non- vaccination sites and that there was an increased risk for sarcoma development with increased numbers of vaccines at a given site. 6.4 Animal carcinogenicity data: Chromium metal powder was tested in rats by intramuscular and intrarenal administration, in mice and rats by intrapleural and intraperitoneal administration, in rats and rabbits by intraosseous implantation and in mice, rats and rabbits by intravenous injection. No increase in tumour incidence was observed in these studies, although most studies had limitations in design, duration or reporting.

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1975:552358 Document No. 83:152358 Biodegradable polymeric article for dispensing drugs. Yolles, Seymour (USA). U.S. US 3887699 19750603, 8 pp. (English). CODEN: USXXAM. APPLICATION: US 1970-102431 19701229.
AB Drugs are incorporated in biodegradable (absorbable) polymers such as **polylactides** and poly(glycolic acid). When the polymeric drug dispenser is s.c. implanted, the drug migrates through the polymer and is controllably released. The rate of release is controlled by choice of polymer, mol. weight, degree of crystallinity, and temperature of preparation Many applications are possible as in diabetic insulin treatment, drugs for **arthritis**, addictive drug antagonists, hormone regulating drugs, and in animals. An example of cyclazocine [3572-80-3] incorporated in poly-L-lactide [33135-50-1] implanted in rats is given.

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L21 67 POLYGLYCOLIDES

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L23 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
2003:491015 Document No. 139:57936 Solid pharmaceutical for parenteral administration. Hansen, Henrik Egesborg; Sabra, Mads Christian; Rasmussen, Thomas Buch (Novo Nordisk A/S, Den.). PCT Int. Appl. WO 2003051328 A1 20030626, 51 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-DK865 20021217. PRIORITY: DK 2001-1901 20011218.
AB A solid pharmaceutical composition for parenteral administration comprises an inner matrix containing at least 1 therapeutic agent, and a biodegradable, and water-impermeable coating covering part of the surface of the composition, wherein the inner matrix disintegrates upon contact with animal tissue or tissue fluids. The coating is made from a material selected from the group consisting of polyesters such as **polyglycolides**, polylactides and polylactic polyglycolic acid copolymers, etc. The inner-matrix may comprise a binder, e.g., mannitol, and the active agent may comprise insulin. Dry amorphous Maltidex H16323 (35 g) was mixed with 35 g human insulin. The mixture was cooled and investigated under a microscope and there was no air entrapment, which also is indicated by the constant torque. The insulin activity before mixing was 99.62% and after mixing 97.52%.

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